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Editorial

The Kveim Test in Sarcoidosis

THE cloud of uncertainty about the validity of the Kveim test in the diagnosis of sarcoidosis seems to be lifting gradually. For some twenty years favorable experiences with this diagnostic procedure have been accumulating in this country [*1–4*] and abroad, particularly in Norway [*5,6*], Denmark [*7*], Great Britain [*8*] and New Zealand [*9,10*]. More than 1,000 patients around the world have now been tested in this way, by intracutaneous injection of suspensions of sarcoidal lymph node or splenic tissue, usually prepared locally.

With preparations of satisfactory specificity and sensitivity, it has generally been found that about three of every four patients with active sarcoidosis respond. In them, a papule is induced at the site of injection which, on punch biopsy performed under local anesthesia four to six weeks after injection, shows epithelioid-cell tubercles similar to those seen in the spontaneously occurring lesions. "False-positive" reactions are uncommon, being exhibited by about 2 per cent of non-sarcoid subjects, when the test is properly performed [*11*].* Unfavorable opinions about the worth of the test may have stemmed, in part, from the use of unsuitable test preparations [*12*]. Until recently, screened test material has been in too short supply for general distribution.

An International Conference on Sarcoidosis took place in Washington, D. C. on June 1–3, 1960, under auspices of the National Academy of Sciences—National Research Council. Among the participants, from ten countries, were epidemiologists, pathologists, microbiologists, immunologists and clinicians of the sundry medical specialties concerned. They reported on considerable numbers of patients observed in their own countries.

The conference formulated a summary statement describing the characteristics of sarcoidosis in the light of what had been learned since the last statement was issued in 1956 by the Committee on Sarcoidosis of the Division of Medical Sciences, National Academy of Sciences—National Research Council. The new formulation takes cognizance of the usefulness of the Kveim test as a histologic means of confirming the diagnosis of sarcoidosis:

"Sarcoidosis is a systemic granulomatous disease of undetermined etiology and pathogenesis. Mediastinal and peripheral lymph nodes, lungs, liver, spleen, skin, eyes, phalangeal bones, and parotid glands are most often involved, but other organs or tissues may be affected. The Kveim reaction is often positive and the tuberculin test often negative. Other important findings are hypercalciuria and increased serum-globulins. The characteristic histological appearance of epithelioid tubercles with little or no necrosis is not pathognomonic; tuberculosis, fungal infection, beryllium disease, and local sarcoid-tissue reactions must be excluded. The diagnosis should be restricted to patients who have consistent clinical and radiologic features together with biopsy evidence of epithelioid tubercles or a positive Kveim test."

The conferees thought it would be helpful to classify cases of sarcoidosis into subacute and

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chronic stages, using a two-year duration as the dividing point. The conference also suggested that active or inactive status of the disease be recorded when possible and, in cases of inactive status, any functional residual impairment in an affected organ.

The summary statement, it will be noted, cautions against acceptance of the diagnosis of sarcoidosis either on clinical or on roentgenologic findings alone. Nor is it enough to find noncaseating tubercles in some tissue or organ, without supporting characteristic clinical findings. Most pathologists practice the same cautious attitude when describing a tissue biopsy specimen which contains epithelioid-cell tubercles. Their readings usually state that the findings are "compatible with but not necessarily diagnostic of sarcoidosis." This, in effect, leaves the final diagnosis to the clinician who correlates the clinical facts with the biopsy findings before he makes a judgment. Now, with wider application of the Kveim test, the pathologist is again being called upon to share more fully in diagnosis.

The Kveim test serves two main diagnostic purposes. First, it confirms the diagnosis of sarcoidosis in patients for whom we have clinical but not histologic data. Second, it helps to differentiate between sarcoidosis and other granulomatous diseases when characteristic epithelioid cell tubercles are found in the tissues by biopsy but clinical ambiguities exist. Here, a positive reaction to the Kveim test can be decisive. Availability of effective Kveim test suspensions would increase awareness of and interest in sarcoidosis and make for earlier recognition.

The question has been asked whether sarcoidosis is the same disease in the various countries. Several approaches to this problem are being explored and in some of them wider use of the Kveim test may be of value. For example, it would be desirable to learn whether patients with sarcoidosis in various countries respond similarly to a standardized Kveim test suspension and whether the source of the sarcoidal tissue makes any difference. Parallel injections of previously calibrated suspensions of each type could bring to light any such disparities.

Kveim testing suspensions prepared from sarcoidal tissues of patients residing in New York City, have been tested in various parts of the United States, Puerto Rico and England on a small scale. Results obtained in these areas do not appear to differ from those encountered in New York City [*11,20,21*]. The fact that Kveim suspension prepared from tissues of a single patient in New York City serves as an effective test agent for patients with sarcoidosis in widely scattered regions suggests that a common primary inciting agent may be at work. If sarcoidosis were, on the other hand, the result of many different agents, varying with the locality, it would be expected that a series of sarcoidal tissues would be required to detect the presence of the disease in different areas.

Nonetheless, some geographically determined differences in mode of onset of sarcoidosis are known. For example, the association of erythema nodosum with the onset of sarcoidosis is very common among young women in Sweden [*13*] and England [*14*]. It is also frequently encountered among women born in Puerto Rico who have migrated to New York City [*15*]. In contrast, erythema nodosum ushers in the disease less frequently among Negroes who constitute the predominant group of persons affected by sarcoidosis in this country. It is apparently not seen at all among patients with sarcoidosis in Japan [*16*]. Why this predilection for erythema nodosum exists among certain nationalities is not known but it may be noted that Swedish women, for example, have been found to be especially prone to exhibit erythema nodosum coincident with the onset of streptococcal infections and tuberculosis as well.

When early asymptomatic hilar node enlargement is disclosed by mass roentgenography, the suspicion of sarcoidosis immediately comes to the fore. Such patients, however, cannot be assigned a definitive diagnosis until histologic corroboration can be obtained. Pre-scalene fat pad biopsy affords a corroboration in perhaps half of these cases, since the tiny lymph nodes in the fat pad communicate with the mediastinal nodes and may contain the epithelioid tubercles quite early in the course. Negative histoplasmin and negative or weak tuberculin tests under these circumstances give additional support to the diagnosis of sarcoidosis.

Ninety per cent of patients with freshly discovered hilar node enlargement due to sarcoidosis respond to the Kveim test [*17,18*]. In approximately 50 per cent of early cases in which no histologic data can be obtained, the Kveim test can often be determinative. Indeed, for the purpose of comparing the incidence

of early cases of sarcoidosis in different countries the Kveim test would seem to be the best tool presently available. When diagnosis becomes definite only with the appearance of enlarged peripheral lymph nodes or of cutaneous lesions which can be biopsied, the delay in time results in inclusion within the diagnosed group of a higher proportion of patients in the later stages of the disease, thus weighting the sample. Such delays also distort the prognosis, which becomes more favorable as earlier cases are introduced. It can readily be understood, then, that valid comparisons between large series of patients with sarcoidosis in various countries must take into account the proportions of patients in each series with early and later manifestations of the disease. The ratio of early to late cases will be determined in large measure by the scale on which mass roentgenography is carried out, and on whether Kveim testing is applied to those persons whose x-ray findings arouse suspicion of the presence of sarcoidosis. Obviously, the Kveim test cannot be used in the manner in which intracutaneous tuberculin or histoplasmin are applied as mass-screening test agents. Obligatory biopsy of the test site makes the Kveim test unsuitable for case finding in the general population. Should the active factor be isolated, it may become possible to place reliance exclusively on the gross appearance of the nodule. A specific serologic test for sarcoidosis would be a great boon.

Methods for preparing conventional Kveim suspensions have not changed since Williams and Nickerson [*19*], Kveim [*5*] and Danbolt [*6*] first published their prescriptions some twenty or more years ago. By this method, sarcoidal lymph nodal tissue or splenic tissue meeting specifications discussed subsequently is ground in a mortar with sterile saline solution to make a 10 per cent suspension. The heavier tissue particles are allowed to settle out and are then discarded. The cloudy particulate suspension which is obtained is then heated to 56°C. for one hour, on two successive days. It is tested for sterility and, with preservative added, is then ready for use. The intracutaneous test is performed in the manner of a Mantoux test, using 0.15 to 0.2 ml. per injection. Any nodule which appears at the injection site, no matter how small, is biopsied after twenty-eight days.

It can be understood that this crude method of preparation results in products differing markedly in the weight of tissue contained in a test dose. Chase [*20*] determined the amounts of alcohol-precipitable material in thirteen vials of conventionally prepared test suspensions solicited from several workers who employed a total of five sarcoidal spleens as tissue sources. The amount of material deposited intracutaneously using a test dose of 0.15 ml. obtained from these vials ranged from 900 to 2,700 μg.

If one chooses to make test suspensions by the conventional method, it would seem necessary to be aware of the unequal losses of tissue which occur during the step of decantation, depending upon the spleen used. To take account of this, the determination of the alcohol-precipitable dry weight in the unprocessed, minced tissues and in the final suspensions would appear requisite. The dry weight figures are only of relative significance since the amounts of hemoglobin, serum protein and other proteins vary from one sarcoidal spleen to another. In assaying the comparative potency of various fractions of the suspension encountered during the purification process, determinations of the alcohol-precipitable dry weights become indispensable.

Not all sarcoidal tissues have proved useful as sources of satisfactory testing material. We have found that only about half of twenty samples of tissue showing granulomatous involvement yielded useful products. Their histologic appearance gave no clues to potency, and at present one can only determine which tissue samples yield effective products through tests on responsive patients. A hazard is the possibility that the sarcoidal tissues may be contaminated with hepatitis virus. Therefore, only a few patients are initially given an injection of suspension stemming from a new tissue source. When safety in this regard is established, wide-scale testing can be begun.

Tissues may have to be rejected either because they do not contain a high enough concentration of the active principle responsible for evoking a positive reaction in a susceptible patient or because they contain other substances which cause non-specific and foreign-body inflammatory changes when injected intracutaneously in all classes of subjects. Even when the granuloma factor is richly present in some of these unacceptable tissues, their non-specific inflammatory contaminants may be strong enough to obfuscate the microscopic picture,

making it difficult to recognize the characteristic epithelioid cell tuberculoid structures of a positive Kveim reaction.

In a series of experiments directed at the standardization and fractionation of Kveim tissue suspensions, Chase and Siltzbach [21] have been able to reduce by more than 50 per cent the alcohol-precipitable dry weight of test suspensions prepared from a sarcoidal spleen. By differential centrifugation and washings, it has been possible to eliminate such inert components as hemoglobin, soluble tissue proteins and serum proteins, fine particulates and some lipids, without essential impairment of the diagnostic competence of the tissue suspensions. Non-specific inflammatory reactions at the site of injection seemed to be reduced by use of the washed preparations.

To obtain uniform preparations and stable suspensions, we have subjected sarcoidal tissues to the high-speed shearing action of motor-driven steel blades as well as to ultrasonic vibration. Steel sieves of fine mesh are used to strain the coarser particles which can then be further reduced in size by a second fragmentation.

Ehrlich [4] has called attention to the great care which must be observed to eliminate cotton lint from the suspensions. Mylar film, non-waterproof cellophane or aluminum foil wraps are used in place of cotton plugs or gauze. It seems advisable to use buffered saline solution and to keep the suspensions from becoming acidic during the heating process to prevent a coarse coagulum from forming.

Since many sources of sarcoidal tissue will be required for large scale Kveim testing, it will be necessary to calibrate untested suspensions against a product which possesses satisfactory potency and quality. For this, patients with known levels of Kveim reactivity are required. Parallel injections are made and gross and microscopic differences in the resulting papule are assessed. The size of the gross papules which develop at the injection sites and the extent of their granulomatous response histologically may appear to be falsely equal in two products if the tests are conducted at maximal concentration of the suspensions. It is therefore necessary to repeat the parallel testing at higher dilutions, which brings out much more clearly any differences between the known and unknown suspensions. In dilution experiments, only test preparations containing small tissue particles which can be dispersed evenly give explicit results.

Once having determined that a suspension has a satisfactory level of the granuloma-inducing factor, one must next ascertain whether the reactions induced are specific. For this, non-sarcoid subjects are tested with the standard and the unknown suspension and if no significant non-specific or granulomatous reaction occurs among the control subjects, the suspension is deemed acceptable as a test agent.

The optimal particle size and concentration for Kveim test suspensions is still under investigation [21]. It can be stated, however, that tissue particles small enough to pass a bacteriologic filter retain their capacity to evoke positive reactions. The previously held view that coarse particles are more effective in producing positive Kveim responses appears open to serious doubt. Our experience indicates that cell-free extracts retain satisfactory activity.

With the sarcoidal spleen we presently employ as a tissue source, we have found a concentration of 3 mg. per ml., delivering 450 μg. of alcohol-precipitable material in a test dose, satisfactory for diagnostic use. This preparation corresponds to about 1,300 or 2,000 μg. of alcohol-precipitable material in a test dose of the conventionally prepared Kveim suspension containing all elements of a sarcoidal spleen.

Criteria for reading the microscopic sections of the Kveim test sites have been defined [4]. At twenty-eight days or longer, discrete, well formed epithelioid cell tubercles with intermixed giant cells and some non-specific inflammatory cells are present when the reaction is positive. Small areas of fibrinoid change, similar to those seen in the spontaneously occurring sarcoid tubercles, may be visible. On the very rare occasions when a papule at the injected site persists and is biopsied after one year or longer, one may see fibrous tissue, with hyaline changes, encapsulating epithelioid cell tubercles. As in the spontaneous lesions of sarcoidosis, the scarring and hyalinization of old test sites may extend into the epithelioid cell center. The process is entirely similar to the scar replacement seen in the healing phases of older lesions of sarcoidosis.

Test sites showing reactions considered to be negative may contain focal collections of inflammatory cells but they can usually be readily distinguished from the tuberculoid structure of the positive Kveim reaction. The non-specific

cellular accumulations may consist of lymphocytes, plasma cells, histiocytes and giant cells of both the Langhans and foreign body type. Occasionally, haphazard scatterings of epithelioid cells in loose arrangements are also seen. When these are present the reaction may be difficult to classify; in such instances, the test is considered equivocal and should be repeated. Repetition of the test often resolves the issue, disclosing either an unequivocally positive or a negative reaction.

The mechanism for the production of the specific papule in a positive Kveim test is not understood. Perhaps the reaction represents a long delayed specific allergic response but support for this hypothesis is yet to come. The Kveim papule in its slow evolution and epithelioid cell tuberculoid morphology reminds one of the papules produced in a positive lepromin test, or in positive beryllium and zirconium patch tests. But it is not clear whether all these reactions have the same pathogenesis. Nor do we know the nature or cellular location in sarcoidal tissue of the active principle responsible for the positive Kveim reaction.

Preliminary histochemical studies of two sarcoidal lymph nodes and tissue from two positive Kveim test sites removed at twenty-eight days have revealed similar staining qualities [*11*]. Both the spontaneous granulomas in lymph nodes and the induced granulomas of the test sites showed positive staining reactions for neutral and acid mucopolysaccharides, phospholipids and acid phosphatase. Both gave negative reactions to stains for fibrin, neutral fat and amyloid. The similarity of the histochemical staining qualities of the lesions in the lymph nodes and in the Kveim test sites, and their common pattern of healing, lends support to the view that Kveim test suspensions contain the same material which is responsible for inciting the granulomas represented by the spontaneously occurring lesions. What gives the Kveim test its special value is its high specificity, in contrast to the non-specific appearance of the spontaneous granuloma of sarcoidosis. As the Summary Statement of the International Conference on Sarcoidosis indicates, such granulomas occur in tuberculosis, leprosy, beryllium disease and in non-specific local reactions caused by chronic inflammatory lesions, malignancies and trauma.

The epidemiologist finds a perplexing problem in sarcoidosis. Its spotty distribution from country to country and also from section to section within any one country is still to be explained.

Patients exhibiting sarcoidosis can be discovered in almost every country if there is an alertness to the possibility. Nobechi [*16*] reported that in Japan only one case of sarcoidosis was diagnosed before and during World War II (1921–1945) and twenty-six cases in the next ten years (1946–1955), whereas in the last five years (1956–1960) sixty-four cases were found. Wide application of mass roentgenography, in the main, accounts for this recent increase. The number of cases may increase still more when a Kveim testing program gets under way. In China, on the other hand, Snapper [*22*] was unable to find a single case of sarcoidosis in the Peking area although he was on the lookout for it over a four-year period just before World War II. Caseation and acid fast bacilli were found so regularly in excised lymph nodes of his Chinese patients that sarcoidosis could not be diagnosed even if it had been present.

In Uruguay, Purriel [*23*] reported that only two cases were diagnosed in 1939, one in 1942, and none subsequently until 1948. Thereafter, with mass roentgenographic surveys, fifty-four cases were found in the city of Montevideo alone and twelve more in the rest of the country.

In Denmark, where sarcoidosis has been studied for many years, Horwitz [*24*] reported that, in all, 900 patients with the disease were attending clinics. How increased interest in the disease can affect prevalence rates was well demonstrated in that country when a sudden influx of newly diagnosed cases of sarcoidosis was reported from North Jutland. It turned out that a physician had chosen sarcoidosis as the subject of his thesis and was personally unearthing material for it from various clinics in that region.

The prevalence rate for Denmark as a whole was 5.5 per 100,000, which may be compared with 11 per 100,000 in Norway [*25*] and 40 per 100,000 in Sweden [*26–28*]. In one rural province of Sweden the rate was 140 per 100,000. Among young men and women throughout Sweden the new case rate for sarcoidosis at present is about equal to that for tuberculosis.

The striking correlation between the prevalence of sarcoidosis and pine forest distribution in the United States was found not to be duplicated in Japan, Switzerland, Uruguay, Scotland [*29*], Denmark or South Africa [*30*]. Among the

armed forces in Switzerland [*31*], 108 men with sarcoidosis were studied; they seemed to come more often from the relatively drier areas of the country.

In a report of a five-year study of 291 patients with sarcoidosis among United States Army personnel, Cooch [*32*] affirmed the pioneer epidemiologic studies of Michael [*33*], Gentry [*34*] and Cummings [*35,36*] and their co-workers. Again, this study brought out the high incidence of sarcoidosis among Negroes, the rate being sixteen times that of Caucasian personnel. Moreover, there was approximately five times the incidence of sarcoidosis among Negroes and Caucasians born in the southeastern states as compared to those born elsewhere in this country. In the United States Navy, with a series of 303 patients with sarcoidosis, Gundelfinger and Britten [*37*] found the disease tenfold more common among Negroes.

Studies involving the armed forces do not, of course, include women, who are somewhat more commonly affected by sarcoidosis than men. In a mass roentgenographic survey conducted in a Health Center district in New York City where the population is predominantly Negro, the prevalence rate of sarcoidosis among women between the ages of twenty and twenty-nine years was 180 per 100,000 [*38*]. This rate exceeded the rate for newly discovered tuberculosis in the same group. Prevalence rates of this high order have been found thus far only among young women in Sweden.

It is not known whether or not the frequency of sarcoidosis is generally increasing. In Sweden, where full data have been available on an annual basis since 1950, the incidence of sarcoidosis has been relatively constant in the face of a precipitous fall in the new case rate for tuberculosis. In other countries with lower sarcoidosis rates, the steady fall in tuberculosis morbidity and mortality may bring to light hitherto unsuspected instances of sarcoidosis, provided mass roentgenography is practiced. With a clear definition of sarcoidosis and its characteristics, and with use of improved diagnostic agents, we may now expect a truer picture of the epidemiology of the disorder to emerge. Further exploration of ecological factors also should become more meaningful.

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Clinical Studies

A Metabolic Myopathy due to Absence of Muscle Phosphorylase*

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THE several patterns of metabolic events that produce energy for muscular contraction are now fairly well understood. The central feature they have in common is the generation of high energy phosphate compounds, particularly adenosine triphosphate (ATP) and phosphocreatine. This synthesis can be accomplished aerobically by the oxidation, in the Krebs' tricarboxylic cycle, of carbohydrate, fatty acids and other substrates, and to a modest extent anaerobically by the formation of lactic acid from glucose or glycogen via the glycolytic or Embden-Meyerhof pathway. During rest and in light exercise, the energy needs are slight, and the recharging of energy-rich phosphate compounds seems to take place mainly through the oxidation of non-carbohydrate substances, while oxidation of glucose is a minor event [*1*]. The concurrent anaerobic utilization of glucose is small, although some lactate tends to be formed even at rest. During forceful muscular activity, the utilization of ATP increases vastly, perhaps as much as several hundredfold [*2*], and accordingly the entire metabolic pattern changes. The aerobic metabolism of rest, including that of glucose, is increased as much as possible, but is limited by the rate of diffusion of fuel and the supply of oxygen. For the remainder, rephosphorylation is accomplished anaerobically by the glycolysis of glycogen, and if this is not adequate, by depletion of the high-energy phosphate stores.

While the biochemical mechanisms which determine the relative intensities of these various pathways are not precisely known, with the onset of exercise there is a transition from the oxidative to the glycolytic pattern of metabolism. Clinically it is impossible to delineate in detail the fundamental mechanics of this shift, although detection of increased quantities of lactic and pyruvic acids in the circulating blood is a satisfactory index of a normal metabolic response.

Recently we have studied a nineteen year old male subject who was admitted because of intense pain in both forearms which developed following heavy lifting. To all outward appearances he was otherwise healthy and had a normal musculature. One feature of his history, initially not apparent to the patient was that, although mild exercise such as slow walking could be tolerated in normal fashion, abnormally rapid fatigue resulted from even moderate exertion. In other words, the transition from minimal to moderate or intense activity could not be bridged, a situation which, if ascribable to a metabolic defect, was suggestive of a subnormal capacity for glycolysis. This was shown to be true by demonstrating that, after such exercise as could be tolerated, the normal increase in plasma lactate did not occur. In this respect the patient closely resembles a patient described by McArdle [*3*]. Furthermore, it was found that work tolerance, studied in the form of treadmill exercise, was greatly improved by the intravenous administration of glucose and certain other metabolites. This suggested that the metabolic block was proximal to the point of entry of glucose into the glycolytic pathway, and might therefore consist of absence of or a defect in glycogen, phosphorylase (or systems associated with it) or phosphoglucomutase. Subsequent biochemical and histochemical studies of the pa-

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tient's muscle showed the complete absence of phosphorylase, without other demonstrable enzyme defects, and an accumulation of muscle glycogen.*

Preliminary notes on some features of this disease have appeared [*4,5*] including a full discussion of the salient chemical and enzymologic features [*6*]. Other workers, too, have independently studied one patient in whom all essential features seem similar [*7–9*]. In the report presented herein a full description of our studies is given, except that we refer to an earlier paper for the technical details of our biochemical investigations [*6*].

CASE REPORT

D. G., a nineteen year old boy of Scotch-Irish descent, was first seen in the University of California Medical Center Hospital (Los Angeles) on December 20, 1957, with painful swelling of the left arm. The previous day, while pushing a stalled automobile, he noted tightness and fatigue in the left arm, followed by numbness about the wrist. Later in the evening this progressed to complete loss of sensation distal to the wrist. There was associated painful "cramping" of the muscles of the forearm and marked venous engorgement and swelling of the soft tissues of the forearm and hand. A similar process evolved in the right arm, but to a much lesser degree. On the following morning, the time of admission, gradual improvement had occurred in all symptoms.

Since childhood the patient had experienced muscular cramping with any excessive exertion. It developed in any muscle or muscle groups of the legs, arms, back or fingers, and lasted for a few minutes to several days. It was not relieved by heat, although on occasion forcible stretching of the muscles as they began to cramp could abort a severe attack. There was no association of cramping with meals or fasting, but muscular movement was somewhat slower and less flexible in the morning or in a cold environment. When tired he was more prone to cramping, but by pacing himself carefully the patient could avoid it. For example, on a long hike up an incline he was forced to rest frequently in order to avoid leg cramps. An episode of cramping of the forearms, similar to that which precipitated his present admission, occurred two years previously and was initiated by an "arm lock" during a wrestling match. Specific and severe muscular cramps had also occurred in the past in the shoulder and chest muscles, paraspinal and abdominal wall muscle groups and in the thighs and calves.

Another symptom, of which the patient was less clearly aware, was the development of "fatigue" or weakness of continuously or intensively exercised muscles. The rate of appearance of muscular fatigue was proportional to the degree of exertion. Hence slow walking on level ground could be tolerated indefinitely, but more rapid walking, running, or climbing a hill induced rapid fatigue in the leg muscles which would "turn to rubber" and occasionally would cramp. Hence when walking up a mild grade at an average pace he was forced to rest about every 150 yards. Two or three minutes of rest would suffice to regain most but not all of his initial strength. He was not dyspneic after this amount of exercise.

The patient first became aware of limited work tolerance at about seven years of age (although it was likely present since birth), when it was recalled that he was unable to run for any distance with other children. Specifically, he recollects a foot race of about 200 yards in which he initially took the lead but began to falter after 50 yards and had to stop at 100 yards because his legs would no longer move. Numerous similar episodes, involving any group of exercised muscles, were recalled. The initial muscular strength apparently was normal. The more strenuous the exertion, the more prompt the appearance of fatigue and the greater the likelihood of development of a cramp. For example, he was never able to perform more than three body "push-ups," or more than eight deep knee bends.

There was no history of fainting, convulsions, generalized or localized neurologic symptoms or visual difficulties. Neither was there any muscular tremor, twitching or systemic symptoms. He was not clumsy, and had never noted diplopia, or fatigue of the eyelids, chewing, swallowing or laryngeal muscles. His birth and early growth and development were entirely normal. He had had several childhood illnesses without sequelae; a tonsillectomy at age five and a mild injury to the left arm at age six. A review of the family history was likewise non-contributory. His mother was an adopted child and nothing was known of her parents. She was a healthy person without muscular symptoms until she died in an accident at the age of twenty-three years. The patient's father, forty-nine years of age, was in good health. He had experienced cramps of the calf muscles related to exertion two or three times, but he had no known limitation of muscular work. Results of an ergograph test of the forearm muscles of the father, made with the circulation occluded were normal. The only sibling, a brother aged eighteen, was in good health and had no history of muscular disorder. An ergograph test on the brother gave normal results. Detailed history of nineteen parental relatives in three generations gave no evidence of the presence of a neuromuscular disorder.

Physical examination upon hospitalization revealed

* We wish to record the paradox that, while the late Dr. Gerty Cori described and characterized several types of glycogen storage diseases as due to deficiencies of various enzymes, she did not encounter any disorders caused by absence of the enzyme phosphorylase, in the discovery of which she played a prominent role.

normal vital signs and a blood pressure of 120/80 mm. Hg in each arm. The patient was a tall, well developed young man measuring 6 feet 2 inches in height and weighing 170 pounds. There was symmetrical cyanosis of both hands and wrists. The veins of the left arm and forearm were markedly distended and did not empty with elevation of the arm. There was diffuse mild swelling of the soft tissues below the elbow, maximal in the hand. There was marked weakness of all motions of the hand and wrist. The forearm flexor and extensor muscles were firm and appeared to be in spasm. They were tender to pressure and marked pain was induced by passive flexion or extension of the wrist or fingers. The right forearm was affected in a similar manner but to a much less degree. The general muscular development was normal and there was no evidence of muscular atrophy or overt hypertrophy. Fasciculations were not seen and percussion myotonia was absent. The tendon reflexes were all normal and pathologic reflexes were absent. The sensory system was intact except for partial loss of pin prick and light touch sensation in the cyanotic left hand. Examination of the viscera was entirely normal.

Laboratory determinations revealed a normal urine, hemoglobin 16.4 gm. per cent, white blood count 12,000 per cu. mm. with a normal differential count, sodium 140 mEq./L., potassium 3.9 mEq./L., chloride 99 mEq./L. and CO_2 25.4 mM/L. The serum non-protein nitrogen was 36 mg. per cent, the fasting blood sugar 90 mg. per cent and the serum transaminase (GOT) 28 units per ml.

Upon rest alone the patient's symptoms subsided within two days, and he has not since had difficulty of a comparable degree, although occasional mild muscular cramping has followed excessive exertion as in the past. He was studied repeatedly on an ambulatory basis. On one occasion, following extensive treadmill exercise and several knee bends and push-ups, the patient reported that twelve hours later he passed red urine on three occasions over a six hour period. Unfortunately none of this urine was obtained for testing, and a similar episode has not subsequently occurred. On November 10, 1958, he was readmitted to the hospital for three days during which time a biopsy specimen of the muscle was obtained from the right lateral thigh under local anesthesia.

METHODS

All *in vivo* studies were performed with the patient and two healthy male controls (twenty-nine and thirty-seven years of age) in the fasting state. Serum lactate was determined by the method of Barker and Summerson [*10*] and pyruvate by the technic of Friedemann and Haugen [*11*] after prompt inhibition of glycolysis in serum with sodium fluoride and chilling to 4°C. Other serum analyses for glucose, creatine, creatinine, proteins, transaminases (SGOT and SGPT) and various electrolytes were made by standard laboratory procedures. An oral glucose tolerance test, with 100 gm. of glucose, was followed by serial determinations of serum glucose, potassium and phosphorus every thirty minutes for three hours. An epinephrine test was conducted using 0.4 ml. of a 1:1000 solution intravenously in normal saline solution, followed by serial serum glucose determinations for three hours.

Exercise during ischemia was studied in the forearm by first occluding the circulation to the right hand with a narrow blood pressure cuff inflated to 200 mm. Hg at the wrist. Venous blood was then drawn from the free-flowing circuit in the antecubital vein and a second cuff was inflated around the right upper arm to a pressure of 200 mm. Hg. The forearm muscles were worked by firmly and repeatedly squeezing a sphygmomanometer bulb one time per second to complete fatigue (usually about forty-five seconds). The amount of air expressed from the bulb was measured and charted on a standard vital capacity machine with rotating drum. An equivalent amount of work during ischemia was done by the two control subjects, and blood was drawn for similar analyses. After completion of the work the cuffs were left inflated for a total of three minutes after which time the upper cuff was released and venous blood was drawn without stasis from the antecubital vein for lactate and pyruvate analyses immediately upon release and two, seven and twelve minutes thereafter.

Ergograph tracings of muscular work ability were made utilizing the muscles of the forearm. With the circulation open a bulb was squeezed firmly once per second and the resulting contraction force was recorded on a slowly moving graph. Work ability during ischemia was tested with a cuff about the right upper part of the arm which was then inflated to a pressure of 200 mm. Hg. The effects of atropine, 0.4 mg., and Tensilon,® 8 mg., each given intravenously within thirty seconds of testing, were also studied.

Ability to exercise was tested by various procedures including the number of deep knee bends and push-ups possible. It was quantitated more closely by walking on a treadmill. In all experiments the slope was inclined at an angle of 10 degrees and multiple tests were made at 2, 3 and 4 miles per hour. Following many separate trials on different days at various rates of walking, 4 miles per hour was selected as the standard test speed because the most reproducible fatigue end points were recorded at this rate. Several normal control subjects could walk for at least one hour at this pace. The fatigue end point was very distinct in the patient. It usually came on suddenly and was manifested by very marked weakness of the thigh and pelvic muscles, leading to near collapse on many occasions.

In conjunction with treadmill exercise various metabolites and electrolytes were infused intravenously during a twenty minute rest priming period and then continuously during exercise. All solutions were administered at a constant rate of 6 ml. per minute with the exception of glycerol and fat emul-

sion, each of which was given at approximately half that rate. Test solutions included normal saline solution ⅙ M sodium lactate, 4 per cent glucose, 10 per cent glucose, 10 per cent fructose, 5 per cent galactose, 5 per cent glycerol in normal saline solution, and fat emulsion in 4 per cent glucose.* All infusions were continued until fatigue was complete (usually three to six minutes) or until it was apparent that obvious benefit was being derived from the test metabolite (usually thirty to sixty minutes). Samples of venous blood were obtained prior to and at preselected periods during exercise. These samples were tested for lactate, pyruvate, glucose, fructose, and sodium and potassium, as indicated. Serum glutamic oxalacetic transaminase (SGOT) and glutamic pyruvic transaminase (SGPT) were measured on two occasions before, during and after exercise.

Oxygen consumption at rest and during work was measured by collection of the expired air in a Douglas bag. The volume of gas was measured and oxygen and carbon dioxide were determined by the Scholander technic. Respiratory quotient calculations were made during several infusions and these were compared with those of a control subject who performed under the same conditions.

RESULTS OF CLINICAL AND LABORATORY DATA

Work Capacity of Forearm Muscles. Early in the course of study of our patient it became apparent that there was a considerable discrepancy between his ability to exercise the forearm muscles when the circulation was flowing freely through the arm and hand and when it was occluded. During mild work, such as squeezing a rubber hand bulb, the non-ischemic forearm muscles performed similarly to those of control subjects. (Fig. 1.) However, when the muscles were made ischemic his work capacity was greatly reduced below that of the ischemic control subjects, although the rate of work output during the first sixty seconds was nearly comparable. (Fig. 1.) The ergograph tracings in Figure 2 also depict the limited work tolerance of the hypoxic muscle. Benefit was not derived from intravenous administration of atropine or edrophonium chloride (Tensilon), each of which was given before occlusion of the arterial circulation to the forearm. Failure of edrophonium to improve work ability made the diagnosis of myasthenia gravis most unlikely.

Various chemical determinations were made on blood obtained from the anticubital vein before and immediately after forearm work during ischemia and at intervals for fifteen minutes

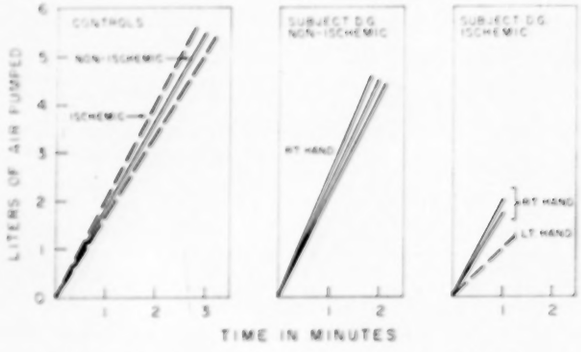

FIG. 1. Work capacity with rubber hand bulb.

after release of the cuff. There was no significant variation, either in the control subjects or in our patient, in the serum levels of calcium, phosphorus, sodium, potassium, chloride, carbon dioxide or SGOT and SGPT. However, there was an obvious difference between the prompt rise in the levels of the lactate and pyruvate in the control subjects and the absence of any such rise in the patient. (Figs. 3 and 4.) Since nearly all of the venous blood draining the forearm came from the long flexor and extensor muscles, it was apparent that under conditions of reduced oxygen tension a considerable amount of lactate and pyruvate was produced in normal muscle. This mechanism was apparently inhibited in our patient, which accounted both for the absence of rise in serum lactate and pyruvate and for his limited work tolerance.

Treadmill Exercise Capacity Before and After Administration of Various Metabolites. Control studies: In order to evaluate the effect of more vigorous muscular exercise the patient was worked on a treadmill at a 10 degree incline. The rate of walking was 2, 3 or 4 miles per hour, and each test was in general a measure of endurance since the end point for the test was complete exhaustion of the exercised leg muscles. When the legs were completely fatigued muscular contraction was still essentially normal in the unworked muscles. All tests were carried out in the morning with the patient in the fasting state. Originally, exercsie was tried at 2 and 3 miles per hour but the results were variable and unpredictable. Usually the patient could walk for fifteen or twenty minutes at 2 miles per hour and from five to twelve minutes at 3 miles per hour. At 4 miles per hour, however, there was a reproducible end point with complete fatigue always by the sixth minute, with an average of 4.2 minutes and a range of three to six minutes.

* Generously supplied as Lipomul by the Mead Johnson Company.

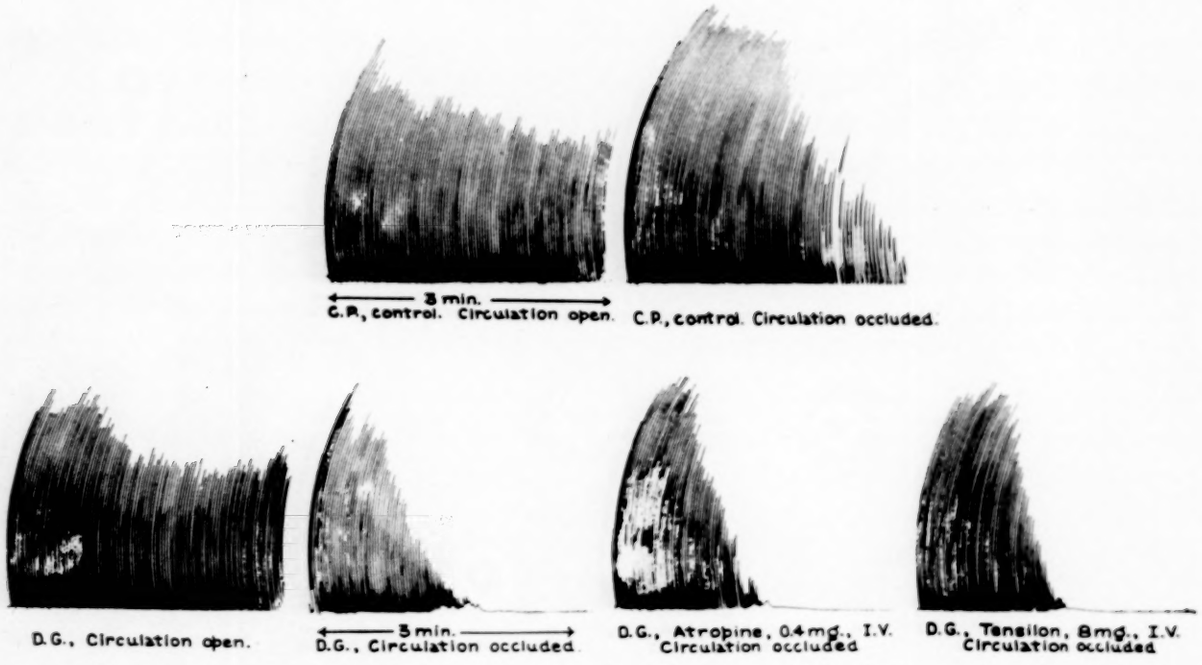

FIG. 2. Ergograph tracings of control subject and patient (D. G.) under conditions indicated (for details see text).

Muscular cramping occasionally developed in the thigh or calf muscles coincident with exhaustion. During these trials the plasma blood sugar averaged 70 mg. per cent (range 60 to 92 mg. per cent). Hence 4 miles per hour was selected as the standard rate with which to compare the effect of various test substances.

Effect of sodium lactate: Continuous infusion of 1/6 M lactate provided a measurable but somewhat unpredictable degree of improvement in work output. (Fig. 5.) The best effort was twenty minutes and the average fifteen minutes.

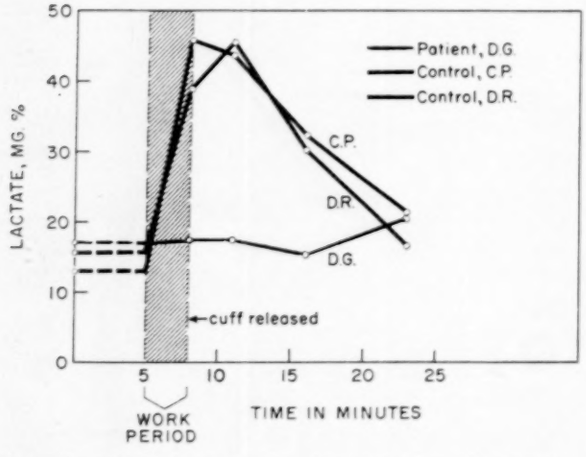

FIG. 3. Antecubital venous blood lactate levels after ischemic forearm muscle work.

The poorest trial was ten minutes, or four minutes better than the best of the control runs. It was interesting to note that lactate markedly improved work tolerance to more than sixty minutes when tested at 3 miles per hour, in contrast to the lack of effect of infusion of either saline solution or sodium bicarbonate when given under similar conditions.

Glucose infusion: Each of these test runs, numbering eight in all, was made while glucose was infused at a constant rate after a twenty minute priming infusion. Marked improvement in ability to exercise was apparent in all tests (Fig. 5), with a range of from thirty-seven minutes to more than sixty minutes (a fifteenfold improvement). The exercise period was arbitrarily discontinued at sixty minutes on three occasions when it was apparent that the subject was still walking easily. Twice the infusion was replaced by saline solution, at twenty and thirty minutes after exercise was begun, and the patient was able to continue for an additional twelve and sixteen minutes, respectively, in the two tests prior to the sudden appearance of exhaustion.

In these studies it was originally thought that the plasma glucose level must be above 160 mg. per cent in order for work improvement to be possible [5]. However, subsequent serial plasma glucose determinations have shown that during

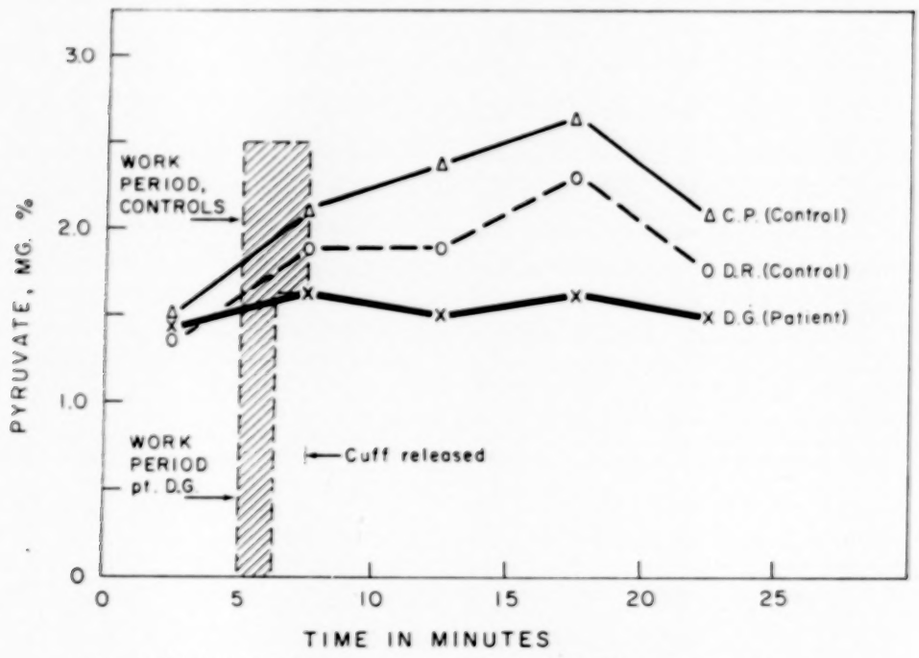

FIG. 4. Venous blood pyruvate levels after ischemic forearm muscle work.

some test runs the glucose did not rise above 110 mg. per cent (from an initial level of 60 mg. per cent) and yet a manifestly improved performance occurred.

Fructose infusion: Treadmill performance during infusion of 10 per cent fructose was equal to or better than that observed with glucose. On the two occasions when this test metabolite was given, exercise was performed with greater ease and the transitory periods of fatigue (the second-wind phenomenon, to be described) were less intense and of brief duration. (Figs. 5 and 6.) Careful simultaneous measurements of plasma glucose and fructose disclosed that the fructose level rose to approximately 40 mg. per cent while the glucose did not change appreciably from a basal level of about 80 mg. per cent. In effect this finding makes it unlikely that the fructose was converted at a significant rate to glucose by the liver and provides reasonably conclusive evidence that fructose can readily transverse the muscle cell membrane, even at low plasma levels, and be utilized by the muscle cell as a major source of energy under some circumstances. This facet of the study has been the subject of a separate report [*5*].

Fat emulsion infusion: A slow thirty minute priming dose and continuous infusion of emulsified fat (Lipomul®) in 4 per cent glucose was given according to the manufacturer's suggestions. Plasma glucose was 95 mg. per cent just before exercise and 76 mg. per cent at the end of the trial. Treadmill exercise was performed with ease for thirty minutes, after which time the trial was arbitrarily discontinued. Subsequently a control infusion of 4 per cent glucose alone, given at the same rate and under the same conditions as the fat emulsion, did not significantly improve exercise tolerance and the patient became exhausted in 7.5 minutes. Plasma glucose levels just prior to exercise and after exhaustion were

FIG. 5. Effect of intravenous infusions on treadmill exercise (4 miles per hour, 10 degree incline).

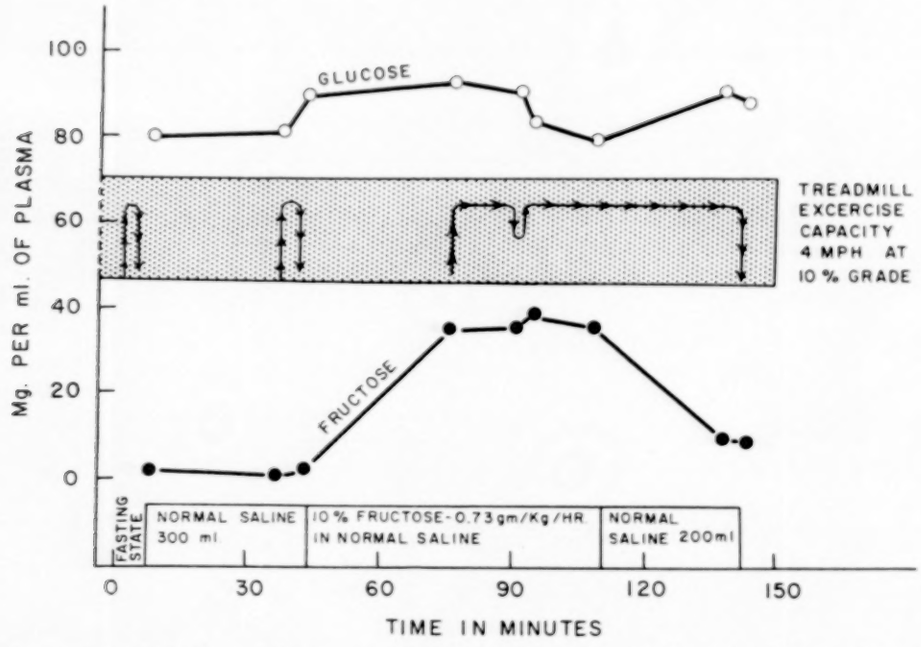

FIG. 6. Beneficial effect of 10 per cent fructose infusion on treadmill exercise. (From: PEARSON, C. M. and RIMER, D. G. *Proc. Soc. Exper. Biol. & Med.*, 100: 671, 1959 [5].)

116 mg. and 71 mg. per cent, respectively. This result suggests that, under the proper circumstances, emulsified neutral fat may be used as an energy source in skeletal muscle. An additive effect of glucose plus the fat is likely in this experiment.

Infusion of other substances: There was no significant improvement in exercise tolerance when normal saline solution alone, 5 per cent glycerol in normal saline solution, or 5 per cent galactose was infused. (Fig. 5.) Sodium bicarbonate (250 ml. of a 5 per cent solution) raised the venous blood pH from 7.42 to 7.53 but did not improve performance. In two trials regular insulin (10 units administered intravenously) when given alone did not significantly prolong work ability. During each test the plasma glucose dropped about 50 mg. per cent to final levels of 32 and 42 mg. per cent. It was not possible to discern any beneficial effect of infusion of glucose plus insulin over the effect of glucose alone on treadmill exercise at 4 miles per hour.

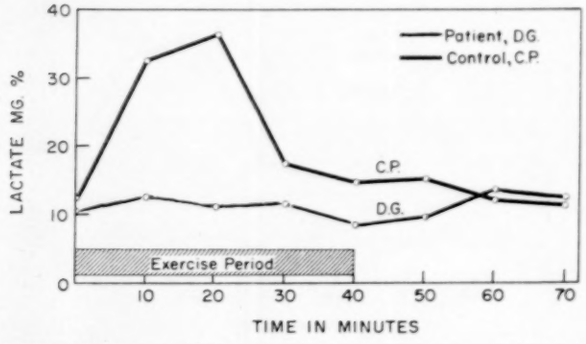

FIG. 7. Venous blood lactate levels during and after treadmill exercise (4 miles per hour, 10 degree incline) with continuous 10 per cent glucose infusion.

Lactate production during treadmill exercise: Plasma lactate levels were measured in a control subject and in the patient at various intervals prior to and during exercise at 4 miles per hour with the continuous infusion of 10 per cent glucose. (Fig. 7.) As in the ischemic forearm muscle experiments, the basal plasma lactate levels were within the normal range. An elevation did not occur in the patient in contrast to a fourfold rise in the control subject's level.

It is somewhat difficult to reconcile the flat lactate curves with the measurable work improvement derived from infused glucose, since lactic acid is almost invariably produced in significant quantity when glucose is the major source of fuel. This would suggest that in the patient a more efficient anaerobic (Krebs) pathway might promptly utilize pyruvic acid before it can be converted into lactic acid.

The "Second Wind" Phenomenon. During the course of the treadmill trials an interesting phenomenon, which we have called the "second-wind," was frequently seen. This event consisted

of a transient period of progressive fatigue and weakness of the exercising muscles which often became quite marked and bordered on complete exhaustion. Most commonly it was seen between four and seven minutes after the start of exercise and it usually lasted for two to four minutes. (Fig. 8.) During this period the patient appeared to expend great physical and mental effort, accompanied by facial grimaces. His legs lagged on the moving treadmill and walking was accompanied by a slapping-type gait. Often, we were about to discontinue the trial when the patient would mention that he was beginning to feel stronger. Within a matter of thirty to sixty seconds all evidences of the previous state of near exhaustion would disappear and he would again walk easily, with little apparent physical or mental effort. This phenomenon was seen at two, three and four miles per hour and occurred erratically. (Fig. 8.) It developed during infusion of any of the metabolites and occasionally two or three "second winds" occurred during a sixty minute exercise trial. Once it appeared at fifty-three minutes and lasted for two minutes and on another occasion it persisted for twenty minutes in a mild form. The most striking feature of this event was the rapid rate and completeness of recovery.

We do not have an adequate physiologic explanation for these episodes. Serial determinations of plasma glucose, lactate, potassium and other electrolytes made during various phases of weakness and after recovery have not shown any consistent change. A type of second-wind event is quite common among long-distance runners, mountain climbers and others engaged in prolonged continuous exertion. It is possible that it signifies a shift in a metabolic pathway under the stress of continuing exertion or it may represent a circulatory readjustment in which there is an increase in blood flow to the exercised muscles and perfusion of a greater number of intramuscular capillaries, many of which remain closed during rest or mild exercise [*12*].

Observations on the Respiratory Rate. During exercise the expected degree of exertional dyspnea was remarkably absent in the patient When complete exhaustion appeared he would present the paradox of marked fatigue but with minimal rise in respiratory rate or depth. The highest rate recorded was 38 per minute immediately after exercise, with a prompt return to 16 to 18 per minute at one or two minutes after exercise. This was in contrast to the breathing

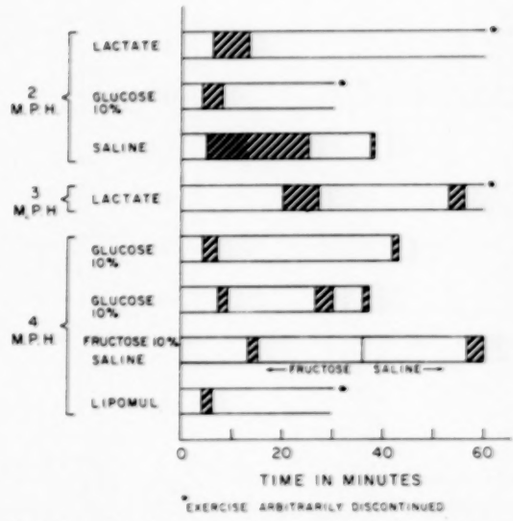

FIG. 8. Second wind phenomenon (shaded areas) as observed during treadmill exercises.

rate of control subjects similarly exercised, who manifested exertional dyspnea for three to five minutes. The patient had a normal degree of tachycardia in response to exertion. It is possible that the limited rise in respiratory rate was related to the lack of elevation in serum lactic acid or other metabolic by-products of normal muscular work.

*Oxygen Consumption and Respiratory Quotient Studies.** With the continuous infusion of 10 per cent glucose, detailed ventilatory studies were made during treadmill exercise of the patient and a healthy control subject of similar body structure and weight. Although it was anticipated that a lesser oxygen debt would be incurred by the patient, none was found. Likewise the respiratory quotient rose in a normal fashion during exercise, from a preexercise value of 0.84 to 1.02 immediately after cessation of work. This response was similar to that of the control subject. The only reproducible abnormality was a falling rate of oxygen consumption during steady walking, from an initial intake of 2,600 cc. per minute to a final level of 1,850 cc. per minute after twenty-five minutes. The oxygen consumption of the control subject remained steady at 2,850 cc. per minute during a similar trial. An adequate explanation for this single discrepancy cannot be given at present, but it may reflect merely the state of physical fitness of these two subjects.

* Drs. B. C. Abbott of the Department of Zoology and J. F. Murray of the Department of Medicine assisted in this phase of the studies.

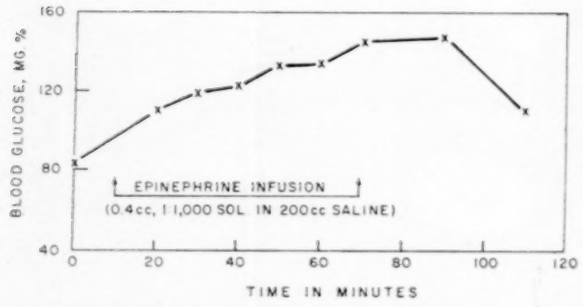

FIG. 9. Effect of epinephrine on blood sugar.

Results of Glucose Tolerance Test and of Epinephrine Infusion. Epinephrine, 0.4 ml. of a 1:1000 solution, was infused in 200 ml. of saline solution over a sixty minute period while the patient was at rest and in the fasting state. Serial blood glucose determinations revealed a normal hyperglycemic response. (Fig. 9.) This response signifies that glucose may be mobilized from hepatic glycogen stores at a normal rate and indicates that the liver enzymes required in this process, i.e., phosphorylase, phosphoglucomutase and glucose-6-phosphatase, are essentially intact. The effect of epinephrine therapy on the ability to exercise was not tested. An oral glucose tolerance test had normal results.

Erythrocyte Lactate Production. Heparinized venous blood was collected without stasis and serial determinations of lactate formation were made prior to and at intervals after incubation at 37°C. There was a progressive accumulation of lactic acid in the plasma which indicated that glycolysis proceeded at a normal rate in the erythrocytes. In Table 1 are tabulated the *in vitro* results obtained on blood from the patient, and for comparison results of a similar study made by McArdle [*3*] on his patient are shown. Both responses are normal. So far as is known the mature erythrocyte does not store glycogen nor does it contain phosphorylase, so that glycolysis occurs solely from the utilization of plasma glucose. The production of erythrocyte lactate signifies that the glycolytic pathway, starting from glucose, is normal in these cells.

TABLE 1
ERYTHROCYTE LACTATE PRODUCTION

Duration of Incubation	Serum Lactic Acid (mg. %)	
	Patient D. G.	Subject G. W. (McArdle [*3*])
½ minute	9.8	3.3
30 minutes	20.1	6.7
1 hour	15.5	11.6
2 hours	28.8	36.4
3 hours	35.6	56.5
4 hours	45.4	...

In Vitro Histochemical Studies. The results of the foregoing *in vivo* experimental studies indicated that there was a gross defect in the breakdown of glycogen to lactic acid in muscles. Moreover, when the circulating glucose or fructose concentrations were increased the level of exercise tolerance was raised. This suggested that the defect might be proximal to glucose-6-phosphate in the Embden-Meyerhof pathway. Attention was thus directed toward the enzymes that are concerned with the immediate breakdown of glycogen, namely "debranching" enzyme, phosphorylase and phosphoglucomutase. A biopsy specimen of the muscle was obtained from the right lateral thigh while the patient was in the fasting state. A similar sample was obtained from a control subject during the course of an operation on the hip. The specimens were rapidly divided and promptly frozen to minus 180°C. in isopentane. The larger sample from each specimen was reserved for biochemical analyses and histochemical determinations were performed on the smaller samples the same day for the presence of glycogen, phosphorylase and "branching" enzyme.

Sections were made from frozen muscle, and from muscle fixed immediately after biopsy in Rossman's fluid. These were stained for glycogen by the Best carmine method and by the Schiff-periodic acid (PAS) technic. By each method there was an obvious increase in the quantity of stainable glycogen over that of the control muscle. (Fig. 10.) The increase was estimated to be three- to fourfold.

Phosphorylase and "branching" enzyme activity were tested for on fresh frozen section material by the methods of Takeuchi [*13,14*]. The striking finding was the complete absence of detectable phosphorylase activity in the muscle from the patient and a normal quantity in the muscle of the control subject. (Fig. 11.) Since the detection of "branching" enzyme apparently depended upon an intact phosphorylase system, the activity of "branching" enzyme in the patient's muscle could not be assessed by this method. Samples of his muscle fixed in 10 per

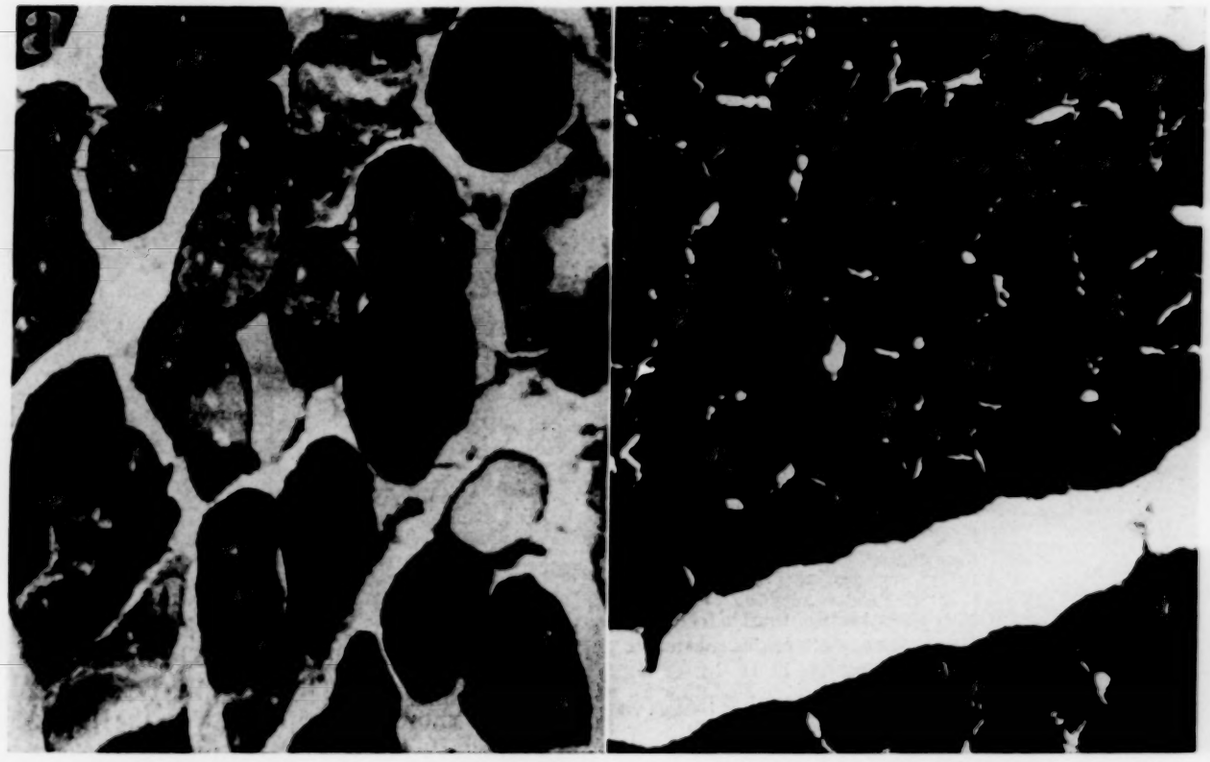

FIG. 10. Demonstration of glycogen content of (a), normal muscle fibers and (b), excessive stainable glycogen in muscle of patient. Best carmine method after fixation in Rossman's fluid. Original magnification × 980.

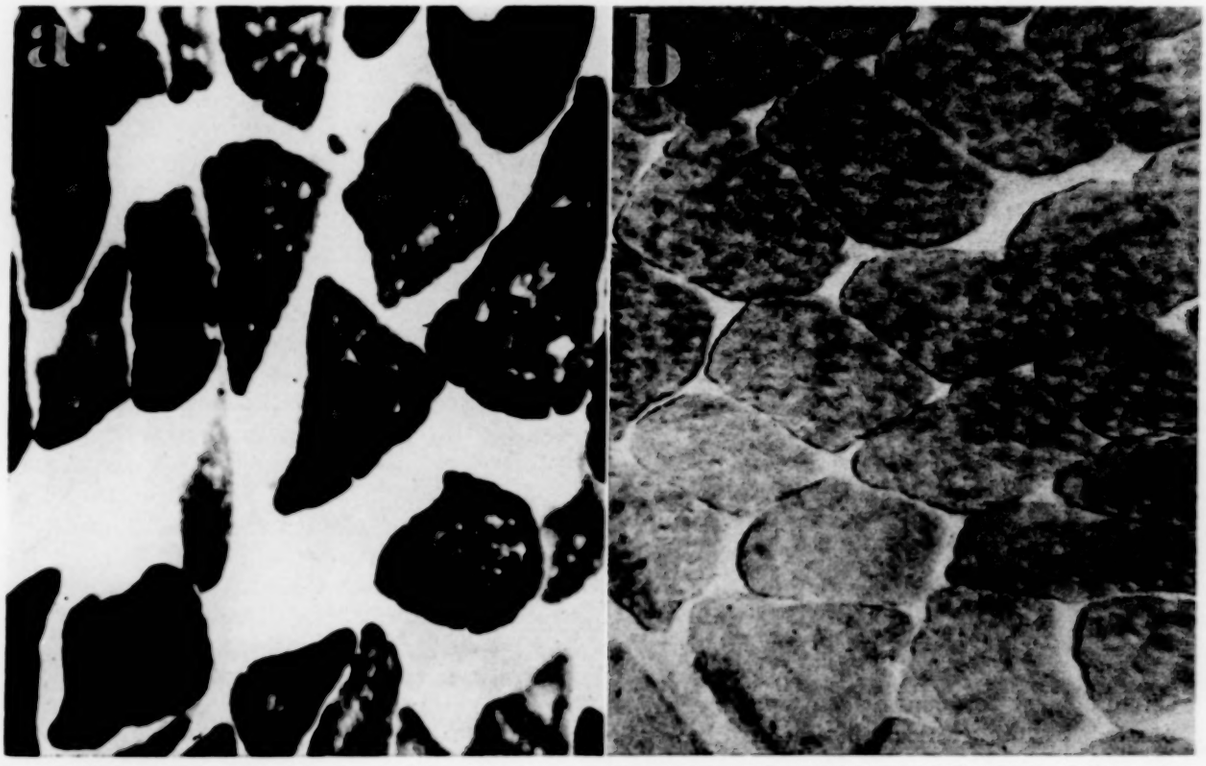

FIG. 11. Histochemical demonstration of phosphorylase activity by the method of Takeuchi [*14*]; (a), in normal muscle fibers; (b), complete absence of activity in muscle of patient. Original magnification × 980.

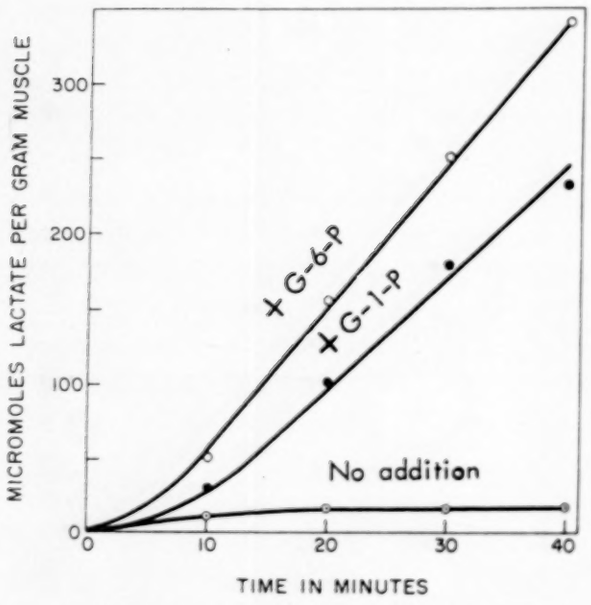

FIG. 12. Glycolytic activity in extracts of muscle from the patient in the presence and absence of various substrates as indicated. (From: MOMMAERTS, W. F. H. M. et al. *Proc. Nat. Acad. Sc.*, 45: 1236, 1959 [6].)

cent formalin and stained with hematoxylin and eosin, revealed an entirely normal microscopic picture.

In Vitro Studies of Metabolism of the Muscle. Since a concise but complete report of the biochemical observations has already appeared [6], this section will, instead, bring a somewhat broader and more explanatory presentation of those data. In view of the tentative conclusions derived from the clinical and experimental results given before, these studies centered upon the following problems: (1) chemical determination of glycogen; (2) test for a possible normal glycolytic mechanism starting with glucose-6-phosphate, but impaired utilization of glycogen; (3) test for the presence of phosphorylase and associated enzymes; and (4) investigation of the mechanism of glycogen synthesis. These four problems will be presented seriatim.

Chemical determinations of glycogen showed, in agreement with the results of the histochemical tests already presented, that the muscle sample was abnormally rich in glycogen, containing a concentration of 4 per cent, while control samples gave values of the order of 1 per cent (within the range considered normal). Therefore, lack of capacity to glycolyse, as indicated by the clinical-physiologic observations, was not due to lack of available substrate. The crucial results, however, were clear enough to overcome these disadvantages. It was found that the rate of lactate production from hexose phosphates, including glucose-1-phosphate, in extracts of the biopsy specimen obtained from the muscle of the patient was not less than was observed in samples of muscle obtained from the control subject. The fact that glucose-1-phosphate was so readily utilized eliminates the possibility of a significant block at the phosphoglucomutase step. By contrast, while extracts of muscle from the control subject could produce lactate from their own or added glycogen, the diseased muscle did not have this ability. (Fig. 12.) In the first few minutes of incubation some production of lactate took place (Fig. 12), but this could be ascribed to the hexose phosphates contained in the tissue as shown by separate analysis, i.e., there was 0.47 μ moles of hexose phosphates per gram of muscle. After this early period, no further glycolysis was detectable. The response of these systems to glucose was not studied in view of the lability of hexokinase under such conditions. Glycolysis in these extracts was thus shown to be limited at the level of formation of glucose-1-phosphate.

The presence of phosphorylase and associated enzymes was studied with the standard methods developed by the Cori school,* which in some experiments were modified so as to detect much smaller amounts of phosphorylase than are usually encountered. The result was that no phosphorylase *a* or *b* could be detected, in keeping with the conclusions indicated by the glycolysis experiments. Remarkably, about normal quantities of phosphorylase kinase and of "phosphate-removing" (PR) enzyme were present. (See Fig. 13.) These two enzymes catalyze the activation of phosphorylase *b* to *a*, and the reversal of this reaction, respectively, and their presence indicates that the enzyme defect is sharply restricted to phosphorylase itself, and does not extend to biologically related enzymes. Furthermore, the accumulated glycogen was found to have a normal branched structure, indicative of the functioning of "branching" enzyme.

The accumulation of glycogen in combination with the absence of phosphorylase focused attention on the mechanism whereby glycogen could be synthesized. At the time of these observations, a phosphorylase-independent pathway for this

* Dr. Barbara Illingworth, Department of Biological Chemistry, Washington University School of Medicine, St. Louis, Missouri, participated in a part of this work.

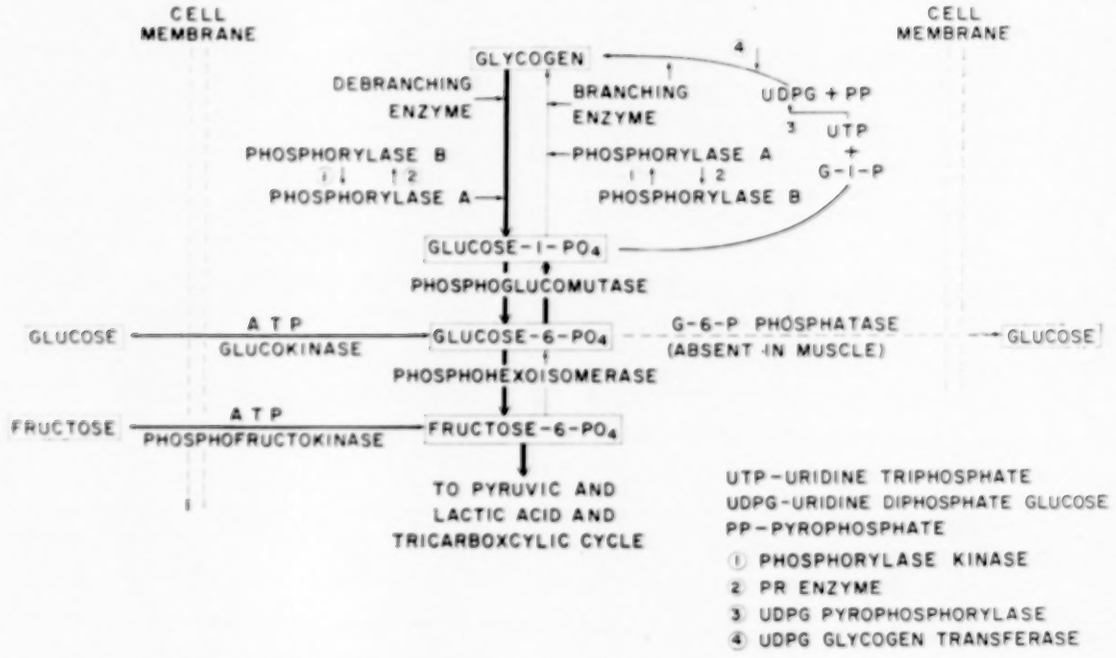

FIG. 13. The Embden-Meyerhof glycolytic pathway, including the position of phosphorylase and associated enzymes and the uridine diphosphoglucose pathway for glycogen synthesis.

synthesis was just in the process of being recognized, based upon the work of Leloir and Cardini [*15*] on the synthesis of glycogen by liver enzymes via the uridine diphosphate (UDPG) pathway. The crucial enzyme of this pathway, UDPG-glycogen transferase, was present in normal amounts in biopsy material.*

A number of additional determinations of various metabolites were performed, but comparison of the sample under study with several specimens from normal subjects revealed no noticeable differences, except for rather low values of lactate and hexose phosphates, which may be a direct consequence of the reduced glycolytic metabolism. Notably, the concentrations of ATP and of phosphorylcreatine were within the normal range.

COMMENTS

The patient described herein illustrates an example of a rare metabolic disorder of skeletal muscle which has now been clearly shown to have as its basis the complete absence of a single enzyme, muscle phosphorylase. Such a disorder, although uncommon, is of considerable interest because of the light it can shed upon the biology and biochemistry of a particular system. Although isolated enzymatic defects have been shown to account for clinical and chemical aberrations in a number of other tissues and organs [*16,17*], the absence of phosphorylase is the first specific defect to be described in skeletal muscle.

Normal resting or minimally active muscle derives most of its energy for metabolism from the oxidation of non-carbohydrate substances such as fatty acids [*1*]. However, even in the basal state a continuous although small amount of glycolytic activity takes place, almost all of which stems from glucose which enters the muscle cell from the circulation. Anbres, Cader and Zierler [*1*] have estimated that about 60 per cent of the glucose taken up by normal resting forearm muscle is degraded to lactic acid. A small and variable amount of the remaining 40 per cent, depending upon the state of the glycogen stores, is deposited as glycogen and the remainder is oxidized to carbon dioxide and water.

During forceful muscular contraction the oxygen supply is insufficient to support the energy demands through the aerobic oxidative mechanisms and further limitations are placed upon this system by the relatively slow rate of entry into the muscle fiber of lipid and carbohydrate nutrients. Hence an alternative source of energy supply is necessary during periods of maximal or

* See preceding footnote, p. 512.

sustained activity, and this source is the stored glycogen. Upon demand, glucose units are promptly cleaved from glycogen by phosphorylation with the aid of muscle phosphorylase and are rapidly fed into the glycolytic pathway. Energy is thus obtained for the recharging of ATP and ultimately for continued muscular contraction.

Normally, the transition from predominantly aerobic to anaerobic (from rest to active) metabolism is smooth and clinically undetectable. Biochemically, however, it may be measured by observing the rise in the concentration of plasma lactate which always occurs in the normal person following exercise [*18*]. Hence lactate formation reflects the magnitude of anaerobic metabolism in contracting muscle. Furthermore, since the concentration of lactate in resting muscle is nearly equal to that found simultaneously in blood [*19*], it is assumed that lactate diffuses from muscle almost as rapidly as it is formed.

Clinically, our patient had a limited exercise tolerance ability, with rapid onset of fatigue in exercised muscles and occasionally the appearance of cramps. Myoglobinuria was probably present on one occasion after very strenuous exercise, but this was not confirmed and pigmenturia has not been detected on several other occasions after lesser exertion. The first real clue that a defect was present in anaerobic metabolism was an absence of the expected rise in the level of plasma lactate after activity, either under aerobic or hypoxic conditions.

Subsequent *in vitro* histochemical and biochemical analyses of muscle disclosed an increased quantity of stored glycogen and complete lack of the enzyme phosphorylase. Depending upon the state of activity or quiescence of the muscle just prior to analysis, phosphorylase normally may be found either in its functionally inactive *b* form or in the active *a* form. (Fig. 13.) Neither was present in this case, but other enzymes which are responsible for the level of active phosphorylase, i.e., phosphorylase kinase and PR enzyme (Fig. 13), were present in normal amounts. An increased content of normally structured muscle glycogen suggested (1) the presence of "branching" enzyme and (2) an alternative pathway for the synthesis of glycogen, since it obviously could not be formed by the phosphorylase route in this case.

Leloir and Cardini [*15*] first described in 1957 an enzyme in liver which could synthesize glycogen from UDPG, which itself can originate from glucose-1-phosphate. Very recently several investigators [*20–23*] have likewise found this pathway to be active in mammalian and other vertebrate muscle. The pathway is schematically outlined in the upper right portion of Figure 13. This uridine nucleotide system has an equilibrium which is far on the side of glycogen formation, as its energy is derived from the splitting of a nucleoside triphosphate.

In the muscle from our patient the UDPG system was found to be intact, hence a reasonable explanation is available for the increase in content of muscle glycogen in this case, although the factors which regulate the level of glycogen deposition are still poorly understood. Exercise, epinephrine and glucagon in the normal subject activate the conversion of phosphorylase from the *b* to the *a* form, at least in the liver, and glycogenolysis promptly ensues [*24a*]. In muscle, exercise and epinephrine enhance phosphorylase activity; hence absence of phosphorylase prevents the periodic partial depletion of glycogen, and excessive glycogen storage results.

The absence of phosphorylase in the patient seemed to be limited to skeletal muscle, a conclusion based upon the following observations: (1) the level of circulating lactate was normal; (2) there was no organomegaly or evidence of hepatic or cardiac dysfunction; and (3) a normal hyperglycemic response occurred to infusion of epinephrine. These features imply that phosphorylase, which is present in nearly all cells and tissues [*24b*], was normal elsewhere. Recent evidence obtained by the use of physicochemical [*24b*] as well as immunochemical methods [*25,26*] in animals has shown that the phosphorylase from heart muscle differs from that prepared from the liver or skeletal muscle. Such observations suggest that there are functional as well as antigenic (and hence structural) differences between the phosphorylases of different tissues. Henion and Sutherland [*25*] have shown that the phosphorylase of liver responds to glucagon, whereas that from muscle does not. On the basis of this evidence it seems likely that a separate gene controls the production of the enzyme in each organ, and in the present case a defective gene is responsible for the enzymatic disorder of skeletal muscle.

The proved absence of phosphorylase in the skeletal muscle fibers of this patient makes him an ideal test subject for a variety of clinical experiments that would otherwise be impossible

to interpret due to the variable effect of glycogenolysis upon the experiment. It has been shown under controlled conditions that our patient can derive significant benefit from infused glucose and fructose. The effect of these hexoses was to improve exercise endurance but neither made very strenuous exertion possible. Fructose was more effective in lower concentration than was glucose [5] (Fig. 6), but the beneficial effect of either was probably due largely to an increased concentration of the hexose in the extracellular fluid, with more rapid diffusion into the muscle fiber. Of further interest was the modest work improvement that was derived from infusion of sodium lactate. This observation suggests that under some circumstances lactate can be utilized by skeletal muscle as a source of energy just as cardiac muscle uses lactate [27]; it implies that the reaction pyruvic acid ⇆ lactic acid, which is catalyzed by lactic dehydrogenase and which has an equilibrium toward formation of lactic acid, can be reversed under appropriate circumstances, i.e., an oxidation of reduced codehydrogenase by the respiratory enzymes.

The mildly beneficial effect of infusion of neutral fat requires further study before any conclusion can be drawn. The lack of effectiveness of infused galactose and glycerol may imply that these metabolites are admitted only slowly or not at all into the muscle fiber, although other explanations are possible.

Strictly speaking, the present case can be considered to be another example of a type of glycogen storage disease. It has been classified as type VI by Stetten and Stetten [24b] in their recent review. Five other types have previously been described [24b,28,29]. Each is rare. The cause of some forms of generalized glycogen storage disease is at present unknown. In others an abnormal glycogen structure points to a defect in "branching" or "debranching" enzyme. The classical von Gierke's disease is due to the absence of glucose-6-phosphatase and is manifested primarily in the liver and kidney. This enzyme is normally absent in muscle.

McArdle [3], in 1951, was the first to describe a patient with a metabolic myopathy which is most likely identical with that found in the present case. His patient, a thirty year old man, showed limited work tolerance and muscular cramping. McArdle noted the failure of muscle to produce lactic acid under hypoxic conditions and the hyperglycemic response to epinephrine therapy. He concluded that his patient suffered from a disorder of carbohydrate metabolism which was most probably due to a failure of glycogenolysis. He did not, however, evaluate the effect of various metabolites on his patient and in the absence of muscle biopsy material he speculated that the metabolic block was similar to that seen in iodoacetate poisoning, namely that there was a defect in glyceraldehyde phosphate dehydrogenase.

Almost simultaneous with our publication of a preliminary report on our patient [4], a note on a similar case was published by Schmid and Mahler [30]. Subsequently, our case was further elaborated upon [6], as was theirs [7]. Schmid and Mahler's patient was a fifty-four year old man who suffered from a chronic, progressive myopathy for thirty-five years. Exercise had become increasingly limited and moderate exertion produced severe cramps and transient myoglobinuria. Lactate was not formed after exercise under ischemic conditions, phosphorylase activity was markedly decreased but not absent in muscle and the UDPG system for glycogen synthesis was present. On histological examination many muscle fibers were found to contain subsarcolemmal blebs or vacuoles which apparently contained glycogen. Larner and Villar-Palasi [8] separately analyzed muscle samples from Schmid's patient and confirmed the very low phosphorylase activity and the normal UDPG pathway, including related enzymes.

Hence three patients have now been described, and two clearly proved, of a metabolic myopathy due to a specific defect in muscle phosphorylase. Schmid and Mahler refer to several other cases that they have seen clinically but it is impossible to evaluate them critically since studies of biopsy specimens from the muscle have not been reported. This condition is rare. McArdle [31] informs us that in the nine years since his original report he has not found another case even though he has conducted clinical laboratory studies on many persons with suggestively similar symptoms. However, more instances may become known now that the condition is more clearly recognized.

Very recently Hers [32] briefly mentioned, during a discussion on glycogen storage diseases, having seen three young children, ages one and a half, three and a half and four and a half years, who upon analysis of liver biopsy material showed a measurable decrease in hepatic phosphorylase activity and a normal muscle

phosphorylase content.* In none of the cases was liver phosphorylase activity totally absent, but rather it was decreased to levels of 10 to 15 per cent of normal. Liver glycogen was elevated in two of the three cases. No clinical data were given. If this enzymatic defect is confirmed by further study these cases may represent the hepatic counterpart of the disorder we have described in muscle. In addition it will provide further evidence for the individuality of phosphorylases in various organs, each of which may be specifically genetically determined.

In none of the cases reported has there been evidence for an inherited disorder. Study of the father and brother of the patient disclosed them to be normal, both clinically and by laboratory testing.

Schmid and Mahler [9] have suggested that it may be therapeutically advantageous to maintain a hyperglycemic state in the presence of adequate insulin. We are not certain whether or not this is a wise recommendation, for although exercise tolerance may be somewhat improved, the hazards of enhancing further and more rapid deposition of glycogen would in the long run far outweigh any transient benefit upon muscle function. Excessive glycogen deposition can apparently cause a progressive structural and functional disorder of the muscle fibers, as was clearly evident in Schmid and Mahler's elderly patient. Our patient has no visible histologic abnormality of his muscle fibers yet, but such may be reasonably anticipated in future years.

SUMMARY

Detailed functional and metabolic studies have been conducted in a nineteen year old boy who had a lifelong history of progressive weakness upon usage of exercised muscles and severe cramps if exertion was intense or prolonged. There was no muscular wasting, and strength during initial exercise was normal. The family history was non-contributory.

Basal serum lactic and pyruvic acid levels were normal. However, there was no rise following treadmill exercise, in contrast to a transitory but significant rise in controls. Ischemic exercise of the forearm muscles was poorly maintained, and no elevation of lactic or pyruvic acid was noted in the venous return from the arm in contrast to a fourfold increase in control subjects.

In the basal state, treadmill exercise at 4 miles per hour (10 degree incline) was limited to about four minutes. Improvement in treadmill exercise tolerance was marked following continuous intravenous infusion of glucose, fructose or lactate but there was no effect from galactose or glycerol. Epinephrine infusion produced a normal hyperglycemic response.

Biochemical and histochemical analyses of thigh muscle revealed a fourfold increase in stored glycogen in the muscle and no reliably detectable phosphorylase. Glycolysis in a tissue homogenate, as indicated by lactate production, was markedly reduced. It was raised to near normal intensity by the addition of glucose-1-phosphate or glucose-6-phosphate. The uridine diphosphate glucose pathway for glycogen synthesis was found to be intact.

This disorder, originally described by McArdle in 1951, is very rare. The deficiency in phosphorylase appears to be confined solely to the skeletal musculature. Because of the increase in stored muscle glycogen the disorder may be classified as another form of glycogen storage disease.

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ADDENDUM

Very recently Schmid and Hammaker [33] have published the interesting observation that two siblings of a patient recently reported on [9] likewise have absence of muscle phosphorylase, but none of thirty-one members in the succeeding generation were affected. This information establishes for the first time a genetic basis for this disease which is apparently due to a "single, completely recessive, rare, autosomal gene."

* We are indebted to Dr. J. W. Weber, Chicago, for calling our attention to this report.

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Familial Hypocalcemia, Latent Tetany and Calcification of the Basal Ganglia*

Report of a Kindred

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IDIOPATHIC hypoparathyroidism and pseudohypoparathyroidism are uncommon entities of obscure etiology. A familial incidence has been reported for both syndromes. The evidence for hereditary transmission is based upon the occurrence of idiopathic hypoparathyroidism in two pairs of siblings, and of pseudohypoparathyroidism in twins and siblings [*1*]. In neither syndrome have cases been reported in more than one generation, and therefore a recessive mode of inheritance has been postulated.

Bilateral symmetrical intracranial calcification of the basal ganglia is rarely found except in conjunction with idiopathic, postoperative or pseudohypoparathyroidism. A familial incidence of basal ganglia calcification has been reported in pseudohypoparathyroidism [*2*]. Familial calcification of the basal ganglia, in the absence of significant abnormalities of serum calcium or phosphorus, has been reported in siblings and in members of more than one generation of the same family [*3*].

This communication describes nine members of the same family, representing three generations, who exhibited a spectrum of abnormalities ranging from a state resembling idiopathic hypoparathyroidism to one of familial calcification of the basal ganglia, without serum calcium abnormality.

CASE 1. A twenty-five year old white, unmarried woman (N. B.) was investigated because of recurrent epileptiform seizures despite anticonvulsant medication. She was first seen at this clinic at the age of sixteen years because of lack of progress in school.

A birth history of traumatic delivery following a difficult labor was obtained. On the third day of life, a grand mal seizure occurred. At the age of one month, following a fall, a second seizure was noted. A diagnosis of idiopathic epilepsy was made following a third grand mal seizure at the age of eighteen months. Between the ages of nineteen months and seven years occasional petit mal episodes were noted but no further major seizures occurred. At the age of seven years the patient was started on continuous anticonvulsant medication of Dilantin® and phenobarbital because of another major seizure. At the age of fourteen years a series of seizures developed which were characterized by staring and inability to speak. Discontinuation of anticonvulsant medication resulted in a gradual lessening of these episodes and she was again seizure-free until her first clinic visit in 1951 at the age of sixteen.

The physical examination at that time showed mental dullness, obesity, shortness of stature, coarse dry skin and a slightly enlarged thyroid gland. Laboratory investigations, including thyroid studies, roentgenograms of the skull and cerebrospinal fluid examination, were within normal limits. An electroencephalogram demonstrated left-sided epileptogenic activity. After anticonvulsant medication was reinstituted she was discharged from the clinic with a diagnosis of post-traumatic epilepsy.

The patient was seen periodically in the Outpatient Clinic for the next five years. During this period there were no significant changes in her symptomatology or physical or neurologic examinations.

In April 1958, at the age of twenty-two years, a grand mal seizure occurred despite her usual maintenance anticonvulsant therapy. The seizure was preceded by several minutes of irrational screaming, and was followed by a postictal state. Examination at that time revealed no essential change in the physical or neurologic examinations. The electroencephalogram was unchanged from previous tracings. The roentgenogram of the skull revealed bilateral calcification of the basal ganglia. The serum calcium was

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TABLE 1

SUMMARY OF LABORATORY DATA (EXCLUSIVE OF CALCIUM AND PHOSPHORUS VALUES) IN NINE MEMBERS OF THE FAMILY

	Case No.								
	I	II	IV	V	VI	VII	VIII	IX	XIII
Blood									
Alkaline phosphatase, King-Armstrong units	8.0	3.7	11.4	15	18	27	13	6.8	9.0
Blood urea nitrogen (mg. %)	10	18	14	14	13	13	13	28	17
Creatinine (mg. %)	0.6	...	0.3	0.4	0.5	0.4	0.3	0.6	...
Uric acid (mg. %)	4.2	3.9	...	...	...	...	...	4.0	...
Cholesterol (mg. %)	247	...	297	...	...	...	...	232	322
Erythrocyte uptake of I^{131} (ET_3 test) (9–17%)	12%	13.3%	14.1%	12.3%	...	...	...	...	...
Protein-bound iodine (μg. %)	6.0	...	6.4	...	...	...	...	...	...
Total protein (gm. %)	8.1, 7.7	7.8	8.3	8.5	7.7	8.1	7.5	7.0	8.3
Albumin	4.7, 4.5	4.3	4.3	5.0	5.0	5.0	4.6	4.7	4.6
Globulin	3.4, 3.2	3.5	4.0	3.5	2.7	3.1	2.8	2.3	3.7
Electrophoretic partition of serum proteins									
Albumin (54–70%)	51, 62	52	50	60	63	55	64	55	51
Alpha-1 globulin (2–5%)	8, 3	6	2	5	3	7	5	2	4
Alpha-2 globulin (7–11%)	13, 9	7	6	8	6	8	8	5	9
Beta globulin (8–14%)	13, 11	14	15	9	13	13	9	14	11
Gamma globulin (9–21%)	24, 15	21	27	18	15	18	14	22	25
Magnesium (1.5–2.5 mg. %)	1.8	...	2.1	1.8	2.1	1.9	1.9	...	2.0
Citric acid (1.3–3.0 mg. %)	1.6	...	2.0	...	...	...	...	...	...
Blood pH (venous)	7.4	...	...	...	...	...	...	...	...
Serology (VDRL)	Negative	Negative	Negative	...	...	...	...	...	...
Spinal fluid								Negative	
Calcium (mg. %)	4.3–4.5	...	4.8	...	...	...	...	4.5	...
Phosphorus (mg. %)	1.7–1.9	...	2.0	...	...	...	...	1.7	...
Protein (mg. %)	19	...	41	...	...	...	...	26	...
Sugar (mg. %)	...	...	63	...	...	...	...	57	...
Urine									
Albumin (sugar and microscopic)	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
17-Ketosteroids (mg./24 hr.)	...	10	9.7	...	...	...	...	11.8	...
24-hour magnesium (50–200 mg.)	...	...	125	29.6	100	65	24	...	...

7.3 mg. per cent, the serum phosphorus 5 mg. per cent, and the total serum proteins 7.7 gm. per cent. Examination of the cerebrospinal fluid and a pneumoencephalogram revealed no abnormalities. The Trousseau sign was positive, but the Chvostek sign was not elicited.

During the next three months the serum calcium ranged from 5.9 to 7.8 mg. per cent despite daily supplements of 100,000 units of vitamin D. The serum inorganic phosphorus varied from 4.4 to 6.3 mg. per cent. The patient continued to complain of tightness of the throat, weakness of the arms, occasional numbness and tingling of the fingers and intermittent vomiting spells. Psychological testing showed a borderline range of intelligence on the Wechsler-Bellevue Scale. She was given intramuscular injections of 200 units of commercial parathyroid extract (Parke-Davis) daily for seven days. Three days after this course of therapy the serum calcium had risen from 7.8 to 8.3 mg. per cent. The serum phosphorus had decreased from 6.1 to 4.5 mg. per cent. Seven days after the course of parathyroid extract the twenty-four-hour urinary calcium had risen from 100 to 178 mg. and the urinary excretion of phosphorus had increased from 247 to 904 mg. Within two weeks following the course of parathyroid extract, the serum calcium and phosphorus returned to pretest levels.

After discontinuing vitamin D therapy for two months, the patient was hospitalized. On admission, the height was 59 inches, the weight 161 pounds, and the arm span 56½ inches. The Trousseau sign was positive and the Chvostek sign not elicited. Slit-lamp microscopy revealed no significant abnormalities. Results of the nose and throat survey were within normal limits. There was no evidence of shortening of the metacarpals or metatarsals. Normal values were obtained for blood sugar, urea nitrogen, uric acid, total protein, cholesterol, protein-bound iodine, alkaline phosphatase, serum magnesium, serum citric acid and venous blood pH. (Table 1.) The urinalysis was normal. Ascending paper chromatography of the urine revealed no abnormalities of aminoacid excretion. No abnormalities were noted in roentgenograms of the chest, gastrointestinal tract, genitourinary tract, gallbladder, spine, paranasal sinuses, hands, feet or long bones. The electrocardiogram showed no prolongation of the Q-T interval and was otherwise normal. The cerebrospinal fluid calcium was 4.5 mg. per cent (concomitant serum calcium 7.7 mg. per cent) and phosphorus 1.7 mg. per cent (concomitant serum phosphorus 5.5 mg. per cent). Dental films showed a relative thickening of the lamina dura and the teeth appeared hyperplastic. There were no unerupted teeth.. An intravenous calcium tolerance test was

TABLE II

RESPONSE OF CALCIUM, PHOSPHORUS AND SUGAR OF THE SERUM AND SPINAL FLUID OF ONE PATIENT (CASE I) TO INFUSION OF 15 MG./KG. OF CALCIUM GLUCONATE

	Serum				Spinal Fluid			
	Calcium (mg. %)	Phosphate (mg. %)	Protein (gm. %)	Sugar (mg. %)	Calcium (mg. %)	Phosphate (mg. %)	Sugar (mg. %)	Protein (mg. %)
Before infusion	7.1	5.8	8.1	82	4.4	1.8	56	19
Hours after infusion								
2	7.3	6.0	...	80	...	...	...	...
4	7.3	5.5	...	96	4.3	1.9	55	19
8	7.5	3.3	7.6	85	...	...	...	...
24	6.3	6.0	...	85	...	...	...	...

performed by the method of Nordin and Fraser (15 mg. per kg. of calcium gluconate in 1 L. of normal saline solution, given intravenously over a four-hour test period). Concomitant examinations of the blood, spinal fluid and urine calcium at the termination of the infusion failed to reveal any change from pre-infusion levels. There was a significant decrease in the serum phosphorus four hours after the termination of the infusion despite a decrease in urinary phosphorus at this time. On the following day a significant rise in the twenty-four-hour urinary output of phosphorus was noted. (Table II.)

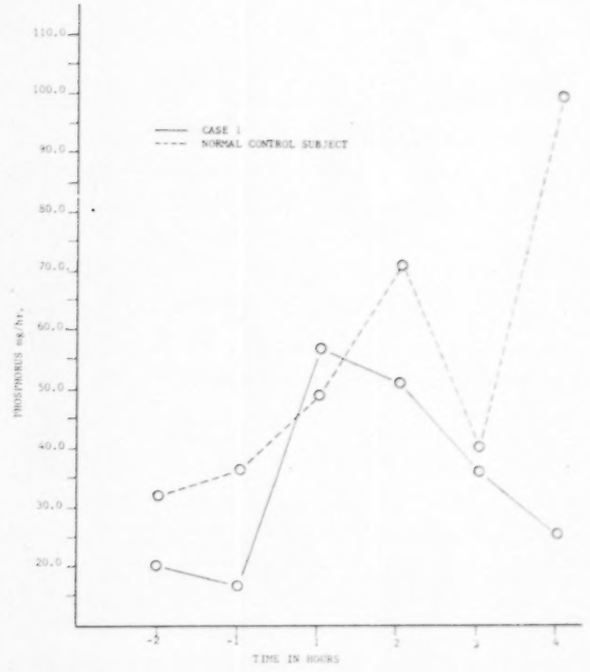

FIG. 1. Case 1. Response of hourly output of urinary phosphorus to 200 units of parathyroid extract given intravenously and a normal control (Ellsworth-Howard test).

Seven days after the conclusion of the intravenous calcium tolerance test, an Ellsworth-Howard test was performed. The parathyroid extract was proved potent by a threefold increase in the rate of urinary excretion of phosphorus by a control subject. A similar threefold increase in the rate of urinary excretion of phosphorus following the intravenous injection of parathyroid extract was obtained in this patient. (Fig. 1.)

During the following six months the highest serum calcium level was 7.6 mg. per cent despite therapy with dihydrotachysterol (AT 10) and vitamin D_2. Two-hour, four-hour and twelve-hour phosphate clearance studies were performed during this six-month period and gave values of 11, 10.4 and 8 ml. per minute, respectively (normal range 8 to 12 ml. per minute). Mental irritability, emotional lability, periodic vomiting spells and complaints of tightness of the throat persisted. The patient voluntarily discontinued anticonvulsant medication and a grand mal seizure promptly occurred.

Comment: This patient was considered an epileptic for many years before a diagnosis of hypoparathyroidism was entertained. The discovery of hypocalcemia, a positive Trousseau sign, and bilaterally symmetrical calcification of the basal ganglia suggested the idiopathic type of hypoparathyroidism. There were no roentgenologic signs of rickets or osteomalacia. There was no evidence of renal insufficiency, steatorrhea, chronic diarrhea or alkalosis. Although the patient was obese, of short stature and showed mental dullness, there was no evidence of brachydactyly or subcutaneous bone formation to suggest pseudohypoparathyroidism. The cri-

teria of Drake for the diagnosis of idiopathic hypoparathyroidism had thus been met but the normal results of the Ellsworth-Howard test failed to conform to the pattern expected in either idiopathic or pseudohypoparathyroidism. The normal phosphate clearance studies were at variance with the low values expected in idiopathic hypoparathyroidism. The symptoms of irritability, mental dullness, tightness of the throat and recurrent vomiting spells suggested a hypocalcemic state. However, the traumatic birth history, the relationship of grand mal seizures to repeated falls, the obvious improvement on anticonvulsant medication, and the prompt recurrence of a typical grand mal seizure following discontinuation of Dilantin and phenobarbital suggest an etiology other than hypocalcemia for the life-long seizure problem.

The inability to raise the level of serum calcium despite prolonged vitamin D therapy was surprising and contrary to the response expected in idiopathic or pseudohypoparathyroidism. That the vitamin D_2 was absorbed is suggested by the hypercalciuria (247 and 207 mg. per twenty-four hours) in the presence of hypocalcemia (7.7 mg. per cent). After nearly one year of continuous vitamin D_2 therapy, the highest serum calcium level recorded was 8.3 mg. per cent and this was obtained after one week of intramuscular therapy with parathyroid extract.

Case II. This forty-five year old white woman (E. B., mother of N. B. [Case I]) was in relatively good health all of her life without previous serious illnesses or significant operations except for surgical pelvic repair. There was no past history of seizures or episodes resembling tetany. The general physical examination was essentially within normal limits. The height was 58½ inches and the weight 158 pounds. The Trousseau sign was positive; the Chvostek sign not elicited. The serum calcium was 7.6 mg. per cent, serum phosphorus 4.4 mg. per cent, serum total proteins 7.1 gm. per cent, and the alkaline phosphatase 3.7 Bodansky units. The urinary Sulkowitch test at this time gave a 2-plus reaction. The urinary output of calcium was 88 mg. per twenty-four hours. The urinary excretion of phosphorus was 541 mg. per twenty-four hours. (Table I.) Roentgenograms of the skull revealed bilaterally symmetrical calcifications of the basal ganglia. Roentgenograms of the chest, long bones and hands were within normal limits. The electrocardiogram was essentially normal and the Q-T interval was not prolonged. The blood urea nitrogen was 18 mg. per cent, serum uric acid 3.9 mg. per cent, and the urinalysis normal. A three day trial of 2 gm. of probenecid, administered daily, failed to lower the serum phosphorus levels. An electroencephalogram revealed abnormality throughout both temporal lobes, with low voltage dysrhythmic activity. During the following year no seizures or tetany developed. The serum calcium level one year after her initial visit was 7.3 mg. per cent, the serum phosphorus 3.9 mg. per cent, and the Trousseau sign remained positive.

Comment: With the exception of a negative seizure history, this patient presented essentially the same picture of hypocalcemia, latent tetany, electroencephalographic abnormality and bilateral symmetrical calcification of the basal ganglia as did her daughter. Further information obtained from the mother indicated that a brother of N. B. (Case I) had died at the age of nine years of a medulloblastoma of the fourth ventricle. Another sibling of N. B. (Case I) was still-born after a full term delivery. Postmortem examination disclosed a grossly enlarged kidney as compared with the other normal one.

Case III. Investigation of the surviving brother (S. B.) of N. B. (Case I) revealed a sixteen year old white boy in excellent health, with no evidence of any specific abnormality. There was no history of seizures or tetany. The physical examination was noncontributory. Chvostek and Trousseau signs were not elicited. The serum calcium was 10.6 mg. per cent and the phosphorus 3.3 mg. per cent. The reaction to the urinary Sulkowitch test was 2 plus. Roentgenograms of the skull showed no evidence of intracranial calcification.

Case IV. This forty-nine year old white man (H. P., brother of E. B. [Case II]) was in relatively good health all his life, except for obesity of long standing, hypertension and a history of duodenal ulcer five years prior to examination. There was no history of seizures or episodes resembling tetany. The physical examination showed marked obesity, hypertension of 180/100 mm. Hg, positive Chvostek and Trousseau signs, and the impression of mental dullness and retardation. He was 62 inches tall and weighed 214 pounds. The serum calcium was 7.1 mg. per cent, serum phosphorus 3.8 mg. per cent and serum proteins 8.3 gm. per cent. The serum citrate was 2 mg. per cent (normal, 1.3 to 3 mg. per cent). (Table I.) One-hour and two-hour phosphate clearance studies were 18 and 18.1 ml. per minute, respectively. (Normal range, 8 to 12 ml. per minute.) The twenty-four-hour urinary excretion of calcium was 18 mg. Serum and urinary magnesium levels were normal as was an electrophoretic partition of the serum proteins. Paper chromatography showed no abnormality of urinary aminoacid excretion. Roent-

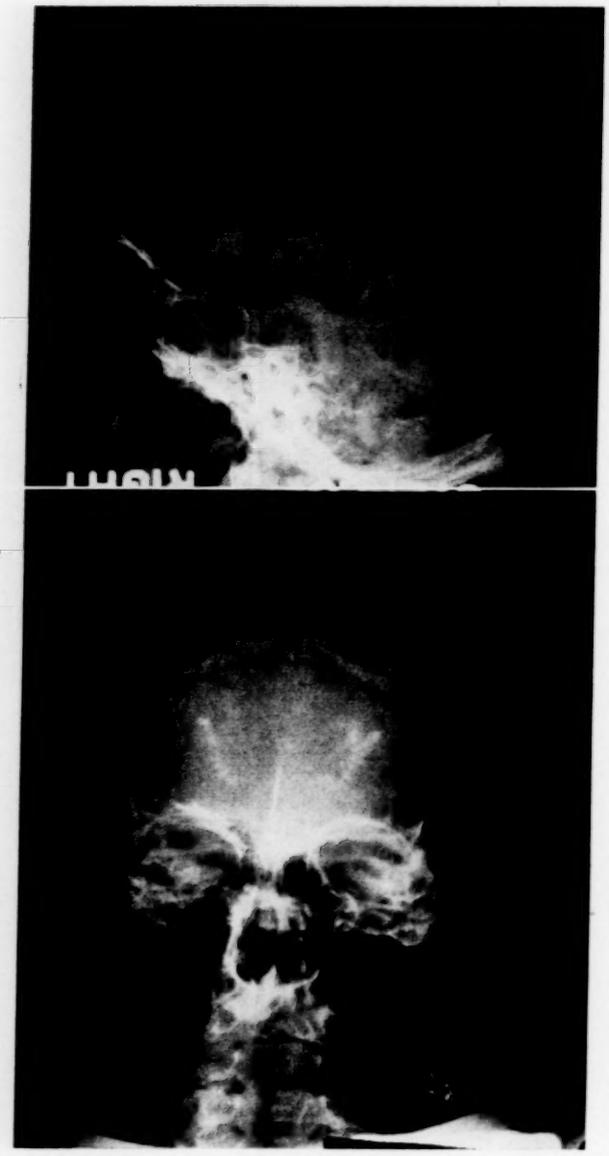

FIG. 2. Case IV. Roentgenograms of the skull showing basal ganglia calcification.

genograms of the skull revealed bilateral symmetrical calcification of the basal ganglia in addition to calcification of the falx cerebri and pineal. (Fig. 2.) The electroencephalogram revealed a temporal lobe dysrhythmia, markedly accentuated by photic stimulation, with high voltage activity. The cerebrospinal fluid calcium was 4.8 mg. per cent at a time when the serum calcium was 7.6 mg. per cent; the cerebrospinal fluid phosphorus was 2 mg. per cent at a time when the serum phosphorus was 4.6 mg. per cent. Other studies included roentgenograms of the chest, gastrointestinal tract and urinary tract, all of which were within normal limits except for a sacral left kidney. The electrocardiogram was normal. The patient was given 100,000 units of vitamin D daily for eight months. At the end of this period the serum calcium and phosphorus levels were 8.2 and 4.4 mg. per cent, respectively. The twenty-four-hour urinary excretion of calcium was 448 mg. and of phosphorus, 789 mg. The Sulkowitch reaction was 4 plus.

Comment: This patient demonstrated a low serum calcium level, calcification of the basal ganglia and signs of latent tetany similar to those in Cases I and II, but unlike Case I the phosphate clearance studies showed an increase on two occasions. There was only slight response of the serum calcium and phosphorus to prolonged vitamin D therapy, despite a marked hypercalciuria (448 mg. per twenty-four hours). The four children of this patient, ages twenty, thirteen, ten and eight years, were investigated with the following findings:

CASE V. The twenty year old daughter (G. P.) of H. P. (Case IV) had no history of a convulsive disorder, tetany or other significant illnesses. The physical examination was within normal limits except for positive Chvostek and Trousseau signs. She was 59 inches tall and weighed 134 pounds. The serum calcium was 8 mg. per cent, serum phosphorus 6 mg. per cent and total proteins 8.5 gm. per cent. Serum and urinary levels of magnesium were normal as was the electrophoretic partition of the serum proteins. (Table I.) The urinary Sulkowitch reaction was 3 plus. The phosphate clearance was 36 ml. per minute (normal 8 to 12 ml. per minute). Roentgenograms of the skull revealed bilateral calcium depositions in the areas of the basal ganglia. An electroencephalogram was normal. The patient was placed on vitamin D_2 therapy, 100,000 units daily for eight months. After this period of therapy the serum calcium was 7.8 mg. per cent and the serum inorganic phosphorus, 5.5 mg. per cent. The twenty-four-hour urinary excretion of calcium was 79 mg. and the phosphorus 495 mg. The urinary Sulkowitch reaction was 4 plus.

CASE VI. This thirteen year old sister (R. P.) of G. P. (Case V) had no history of seizures, tetany or other significant illnesses. The physical examination was non-contributory. The height was 60½ inches and the weight 123 pounds. The Trousseau and Chvostek signs were not elicited. The serum calcium was 9.4 mg. per cent; the serum inorganic phosphorus 3.5 mg. per cent. The total serum proteins were 7.7 gm. per cent. Serum and urinary magnesium levels were normal. (Table I.) The Sulkowitch reaction was 2 plus. The phosphate clearance was 17 ml. per minute. Roentgenograms of the skull revealed bilateral calcification of the basal ganglia. The electroencephalogram demonstrated an unstable record with increased sensitivity to photic stimulation. Eight

months later the serum calcium and inorganic phosphorus levels were essentially unchanged.

CASE VII. This ten year old sister (B. P.) of R. P. (Case VI) had a history of a febrile convulsion during infancy, but no recurrence of seizures or signs of tetany since that time. The physical examination was within normal limits except for positive Chvostek and Trousseau signs. Her height was 56 inches and her weight 122 pounds. The serum calcium was 7.8 mg. per cent, the serum phosphorus 8 mg. per cent, and the total proteins 8.1 gm. per cent. Serum and urinary levels of magnesium were normal. (Table I.) The urine Sulkowitch reaction was 3 plus. The phosphate clearance was 17 ml. per minute. Roentgenograms of the skull revealed bilateral symmetrical calcifications in the region of the basal ganglia. The electroencephalogram showed marked sensitivity to photic stimulation and was considered atypical for this age group. After eight months of therapy with vitamin D_2 in a dosage of 100,000 units daily, the serum calcium was 8.2 mg. per cent and the phosphorus 6.7 mg. per cent. The twenty-four-hour urinary excretion of calcium was 126 mg., and of phosphorus 468 mg. The Sulkowitch reaction was 4 plus.

CASE VIII. This eight year old sister (T. P.) of B. P. (Case VII) has a negative past history for serious illness, convulsions or tetany. The physical examination was within normal limits. The height was 47 inches and the weight 57 pounds. Chvostek and Trousseau signs were not elicited. The serum calcium was 10.2 mg. per cent, the serum inorganic phosphorus 5.2 mg. per cent. Serum and urinary levels of magnesium were normal. An electrophoresis of the serum proteins was normal. The urine Sulkowitch reaction was 3 plus. The phosphate clearance was 10.8 ml. per minute. Roentgenograms of the skull demonstrated no intracranial calcification. The electroencephalogram was essentially normal.

Comment: The maternal uncle of the propositus and two of his four children demonstrated essentially the same clinical picture as Cases I and II. In addition, his thirteen year old daughter had calcification of the basal ganglia in the absence of abnormalities of serum calcium. All except the normal eight year old daughter had an increased phosphate clearance, in the range usually associated with parathyroid hyperfunction.

CASE IX. This thirty-seven year old brother (M. P.) of E. P. and H. P. (Cases II and IV) had no history of seizures, tetany or other significant illnesses. The physical examination was within normal limits except for a positive Trousseau sign. The Chvostek sign was not elicited. The height was 66 inches and the weight 140 pounds. Results of the neurologic examination were negative except for a suggestion of slowness of motor activity and mentation. The serum calcium ranged from 6.6 to 8 mg. per cent, the serum phosphorus from 4.1 to 4.5 mg. per cent and the total serum proteins from 7 to 7.4 gm. per cent. The urine Sulkowitch reaction was 3 plus. The twenty-four-hour urinary excretion of calcium was 76 mg., of phosphorus 619 mg. (Table I.) Roentgenograms of the skull showed bilateral symmetrical calcifications of the basal ganglia. (Fig. 3.) The electroencephalogram showed a diffuse dysrhythmic response to photic stimulation. The cerebrospinal fluid calcium was 4.4 mg. per cent (concomitant serum calcium 7.1 mg. per cent), the cerebrospinal fluid protein 26 mg. per cent. Psychological testing revealed an average range of intelligence, but some defect in retentive memory. The patient received no specific therapy. Seven months later the serum calcium was 7.7 mg. per cent, the serum phosphorus 5 mg. per cent. The phosphate clearance was 16.7 ml. per minute.

FIG. 3. Case IX. Lateral roentgenogram of the skull showing punctate calcifications in the region of the basal ganglia.

CASE X. This thirty-five year old brother (R. P.) of E. B., H. P. and M. P. (Cases II, IV and IX) gave an essentially negative history. The physical examination was within normal limits; and Chvostek and Trousseau signs were not elicited. The height was 64 inches and the weight 138 pounds. The serum calcium was 10.8 mg. per cent, the serum phosphorus 3.3 mg. per cent; the serum proteins were normal. There was no evidence of intracranial calcification on roentgenograms of the skull.

CASE XI. This forty-three year old sister (M. D.) of E. B., H. P., M. P. and R. P. (Cases II, IV, IX and X)

had a history of epilepsy since childhood and had been hospitalized at another hospital for investigation of a coin lesion of the lung. This was subsequently resected and found to be a hamartoma. During this hospitalization, at age forty-one, roentgenograms of the skull were taken. The films were reviewed by us and showed bilateral symmetrical calcification of the basal ganglia, and calcification of the falx cerebri and pineal. The serum calcium and phosphorus levels were reported as normal. An electroencephalogram was interpreted as showing evidence of a latent epileptogenic disorder. No further information was obtainable on this patient.

CASE XII. This seventy-three year old father of E. B., H. P., M. P., R. P. and M. D. (Cases II, IV, IX, X and XI) had an essentially negative past history for serious illnesses, convulsive seizures or suggestive symptoms of tetany. The physical examination was within normal limits except for bilateral immature cataracts. The height was 59 inches and the weight 165 pounds. Chvostek and Trousseau signs were not elicited. The serum calcium was 9.7 mg. per cent, the serum phosphorus 3 mg. per cent; the serum proteins were normal. Roentgenograms of the skull showed calcification of the pineal, the petroclinoid ligaments and the internal carotid arteries, but no other evidence of abnormal intracranial calcification.

Comment: Since the father and grandfather of the patients in Cases I to XI exhibited no abnormality, an attempt was made to investigate the maternal side of the propositus and her family. The grandmother of N. B. (Case I) died at age sixty years of a cerebral hemorrhage, and is said to have been mentally dull and subject to convulsions for a number of years prior to death. No autopsy data are available. Information was obtained on three of her sisters. One sister, aged sixty-three, has a history of seizures and a son is said to have had convulsions and mental retardation. A second sister, aged fifty-nine, was reported to be in good health. A third sister had recently died at another hospital and the following data was obtained:

CASE XIII. This seventy-three year old maternal great-aunt (R. H.) of N. B. (Case I) was admitted to another hospital because of congestive heart failure following a cerebral thrombosis. There was no history of seizures or tetany. Roentgenograms of the skull were reported as showing extensive bilateral symmetrical punctate calcifications in the region of the basal ganglia. The serum calcium ranged from 6.4 to 7.2 mg. per cent, the serum phosphorus from 3.2 to 4.2 mg. per cent. After sustaining a myocardial infarction, she died after one month of hospitalization. At postmorten examination parathyroid tissue could not be demonstrated.

Comment: The presence of a hypocalcemic state and bilateral calcification of the basal ganglia, and failure to demonstrate parathyroid tissue at autopsy, places this member of the family in the category of cases classified as idiopathic hypoparathyroidism.

COMMENTS

Of thirteen members of this family group, nine were shown to have abnormal intracranial calcifications. In addition, asymptomatic hypocalcemia and latent tetany was demonstrated in seven of the nine members. (Fig. 4.) Five members of this family were observed for a period of eight months to two years and were found to have chronic hypocalcemia, hyperphosphatemia and latent tetany. No evidence of rickets, osteomalacia, renal insufficiency, alkalosis or chronic diarrhea was noted. Therefore the criteria for idiopathic hypoparathyroidism set forth by Drake appeared to have been met. Although these patients were short, obese, mentally dull and had short stubby fingers, the absence of brachydactyly or subcutaneous bone formation or calcification eliminated the diagnostic label of pseudohypoparathyroidism. The normal response to the Ellsworth-Howard test and the lack of significant rise of the serum calcium level following a course of intramuscular parathyroid extract in N. B. (Case I) was contrary to results expected in idiopathic hypoparathyroidism. The serum calcium levels in the hypocalcemic members of this family were considerably higher than the levels usually reported in idiopathic hypoparathyroidism. The range in these cases was 6.5 to 8.2 mg. per cent with a mean value of 6.91 mg. per cent. The serum inorganic phosphorus levels in our group of cases were somewhat lower than those usually reported in idiopathic hypoparathyroidism. Serum phosphorus levels in the adult patients studied ranged from 3.2 to 6.3 mg. per cent with a mean value of 4.55 mg. per cent. The three children studied (ages thirteen, ten and eight years) had phosphorus levels ranging from 3.5 to 8.0 mg. per cent with a mean value of 5.56 mg. per cent. Serum phosphorus levels of less than 5 mg. per cent in adults and less than 7 mg. per cent in children are seldom found in idiopathic or pseudohypoparathyroidism [*1*].

Symptoms of tetany were questionable in the

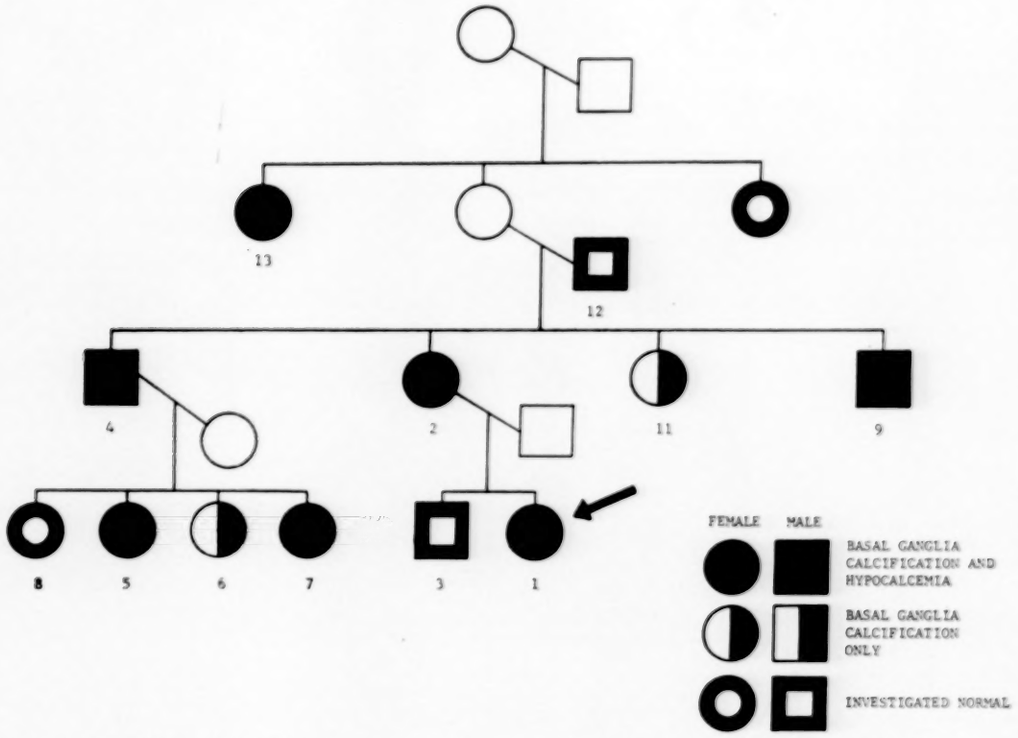

FIG. 4. Simplified genetic diagram of the reported kindred. The propositus is indicated by the solid arrow.

propositus and absent in the other subjects with hypocalcemia. That the ionizable fraction of serum calcium was reduced is suggested by the consistently positive Trousseau signs elicited in all the patients with hypocalcemia. The unreliability of the Chvostek sign and the urinary Sulkowitch reaction as indicators of hypocalcemia was demonstrated repeatedly. (Table III.)

No significant rise in serum calcium levels was demonstrable after the administration of large doses of vitamin D_2 for eight months to two years in the four treated patients with hypocalcemia. This is in contrast to the expected response in idiopathic hypoparathyroidism by approximately the fourth month of therapy [*1*]. The marked rise in urinary output of calcium following vitamin D therapy (276 to 448 mg. per twenty-four hours), despite concomitant hypocalcemic serum levels, suggests a normal renal response to increased calcium absorption but inability to utilize the increased absorbed calcium to elevate the serum level. This phenomenon has been commented upon by Litvak et al. in relation to vitamin D_2, resulting in a decrease in tubular reabsorption of calcium [*4*].

The phosphate clearance studies in Cases IV, V, VI, VII and IX gave results similar to those reported in states of parathyroid hyperactivity. The phosphate clearance in Case I was within the normal range. Contrary to the uniformly decreased phosphate clearance with only slight overlap into the normal range reported in hypoparathyroidism [*5*], repeat clearance studies in all but Case I showed consistently high values, in the hyperparathyroid range. (Table III.)

R. H. (Case XIII), who lived for seventy-three years without overt signs of tetany, was found to have calcification of the basal ganglia and hypocalcemia during an unrelated terminal illness and had no demonstrable parathyroid tissue at autopsy. This, too, is a most unusual course for idiopathic hypoparathyroidism. The oldest patient in Bronsky's extensive review of fifty cases of idiopathic hypoparathyroidism was fifty-four years at the onset of symptoms [*1*].

The occurrence of this syndrome in three generations of the same family is in contrast to idiopathic hypoparathyroidism in which no cases have been described in more than one generation, and at most only suggestive evidence has been presented for its occurrence in two generations [*1*].

Because of the many atypical features men-

TABLE III

SUMMARY OF SIGNIFICANT ABNORMAL FINDINGS IN NINE MEMBERS OF THIS FAMILY AS COMPARED WITH FOUR UNINVOLVED MEMBERS

Case No.	Age (yr.) and Sex	Serum (mg. %)				24 Hour Urine (mg.)		Trousseau(T) and Chvostek(C) Tests	Basal Ganglia	Electroencephalogram	Renal Phosphate Clearance (ml./min.)
		Calcium		Phosphorus		Calcium	Phosphorus				
		High	Low	High	Low						
I	27,F	8.3*	6.8	6.3	4.5*	67–228	241–904	T+ C−	Calcified	Temporal lobe dysrhythmia	11.0 10.4 8.0
II	45,F	7.6	7.3	4.4	3.9	88	541	T+ C−	Calcified	Bilateral temporal lobe, low voltage dysrhythmic activity	...
III	16,M	10.6	...	3.3	...	...	...	−	Negative	...	...
IV	49,M	7.6	7.1	4.6	3.8	230	920	T+ C+	Calcified	Temporal lobe dysrhythmia, markedly aggravated by photic stimulation	18.0
V	20,F	8.0	7.2	6.0	4.3	...	...	T+ C+	Calcified	Normal	36.0
VI	13,F	9.4	...	3.5	...	...	...	−	Calcified	Photic sensitivity, unstable record	17.0
VII	10,F	7.8	...	8.0	...	...	...	T+ C+	Calcified	Sensitivity to photic stimulation, atypical record	17.0
VIII	8,F	10.2	...	5.2	...	...	...	−	Negative	Normal	10.8
IX	37,M	8.0	6.6	5.0	4.1	76	619	T+ C−	Calcified	Dysrhythmic response to photic stimulation	16.7
X	35,M	10.8	...	3.3	...	...	...	−	Negative	Not performed	...
XI	43,F	Normal		Normal		...	...	...	Calcified	Latent epileptogenic disorder	...
XII	73,M	9.7	...	3.0	...	...	...	−	Negative	Not performed	...
XIII	73,F	7.2	6.5	4.2	3.2	...	...	...	Calcified	...	...

*After intramuscular administration of parathyroid hormone for one week.

tioned, the seven members of this family demonstrating a syndrome of ectopic calcification and chronic hypocalcemia do not appear to correspond to the classification either of idiopathic or pseudohypoparathyroidism.

Two members of this family (Cases VI and XI) had calcification of the basal ganglia as the only significant abnormality. (Table III.) No demonstrable abnormalities of serum calcium, serum phosphorus or neuromuscular irritability were present. Palubinskas and Davies [*3*] drew attention to the familial occurrence of calcification of the basal ganglia in apparently normal people without anomalies of stature, brachydactyly, subcutaneous bone formation or serum calcium or phosphorus abnormalities. They described six members of a family, representing two generations, who demonstrated calcification of the basal ganglia. However, latent abnormalities of phosphorus balance and a suboptimal response to the Ellsworth-Howard test were shown in two affected members. Thus, had only Cases VI and XI been investigated, they could have been classified in the category of familial calcification of the basal ganglia. The occurrence of calcification of the basal ganglia in seven other members of this family with associated hypocalcemia suggests a close relationship between this family group and that described by Palubinskas and Davies.

Although seven members of this family were found to have electroencephalographic abnormalities, only the propositus suffered overt convulsions. (Table III.) Temporal lobe dysrhythmic activity was demonstrated both in the propositus and her mother (Case II). H. P. (Case IV) showed dysrhythmic responses to photic stimulation as did two of his daughters (Cases VI and VII) and his brother M. P. (Case IX). In view of the cerebral dysrhythmia, photic sensitivity, chronic hypocalcemia and latent tetany, it is surprising that overt convulsive seizures or tetany had never developed in these latter four patients. The assumed association between convulsive seizures and hypocalcemia in idiopathic hypoparathyroidism may be less clear-cut than previously thought. One may speculate that the incidence of cerebral dysrhythmia in families of patients with idiopathic hypoparathyroidism may be greater than expected in a random population. In the family herein reported a genetically transmissible epileptogenic trait may well be independent of the suspected genetic defect in calcium metabolism.

TABLE IV

TABULATION OF SIMILARITIES BETWEEN THE AFFECTED MEMBERS OF THIS FAMILY AND OTHER SYNDROMES OF ECTOPIC CALCIFICATION WITH OR WITHOUT HYPOCALCEMIA

Syndrome	Familial Incidence	Ectopic Calcification		Normocalcemia	Hypocalcemia	Remarks
		Subcutaneous	Basal Ganglia			
Familial basal ganglia calcification	+		+	+		Normal stature
Cases VI and XI	+		+	+		Short stature, no brachydactyly
Pseudo-pseudohypoparathyroidism	+	+		+		Short stature, brachydactyly
Tanz Case 2 [10]	+	+	+	+		Sister with pseudo-pseudohypoparathyroidism
Palubinskas and Davies Case III [3]	+	+	+	+		Spontaneous reversion of pseudohypoparathyroidism to pseudo-pseudohypoparathyroidism followed by basal ganglia calcification
Pseudohypoparathyroidism	+	+	+		+	Short stature, brachydactyly
Cases I, II, IV, V, VII and IX	+		+		+	Short stature, no brachydactyly
Case XIII	+		+		+	Absence of parathyroids at autopsy
Idiopathic hypoparathyroidism	+		+		+	Normal stature

This family group thus demonstrates a syndrome of familial ectopic calcification associated with either normocalcemia or hypocalcemia. Parathyroid insufficiency was not demonstrated in the living patients; indeed, the phosphate clearance studies in some of them were in the range of parathyroid overactivity. In the autopsy case, parathyroid tissue was not identified. Therefore this group of cases appears to represent transitional states between normocalcemic familial calcification of the basal ganglia and the hypocalcemic ectopic calcification states of idiopathic hypoparathyroidism and pseudohypoparathyroidism.

Two other recently reported cases deserve comment since they also appear to represent transitional states. Palubinskas and Davies [3], in their review of calcification of the basal ganglia, described a patient with well documented pseudohypoparathyroidism who spontaneously reverted to a normocalcemic state without therapy. During this period of spontaneous "cure," calcification of the basal ganglia developed. Thus the patient presented the clinical picture of so-called pseudo-pseudohypoparathyroidism with manifestations of calcification of the basal ganglia. The development of intracranial calcification after the serum levels of calcium had returned to normal suggests a continuing abnormality of calcium metabolism in the presence of compensatory parathyroid activity.

Tanz [6] reported two cases in one family of what was termed pseudo-pseudohypoparathyroidism on the basis of physical appearance and the demonstration of subcutaneous bone formation and brachydactyly. One of these patients also had calcification of the basal ganglia. This either represents the first report of calcification of the basal ganglia in a case of pseudo-pseudohypoparathyroidism, or a situation analogous to that reported by Palubinskas and Davies of a normocalcemic state of pseudohypoparathyroidism resulting in the picture of pseudo-pseudohypoparathyroidism. The similarities between these two cases, familial calcification of the basal ganglia, the family reported here, and the classic states of idiopathic and pseudohypoparathyroidism are summarized in Table IV.

The features common to this group are a familial incidence and the presence of ectopic calcification either in subcutaneous tissues or in the basal ganglia. The parathyroid glands are implicated only in those patients in whom a normal level of serum calcium cannot be maintained. The relatively few cases of idiopathic

hypoparathyroidism in which absence of parathyroid tissue has been demonstrated at autopsy, the notoriously late recognition of hypoparathyroidism despite symptoms for years, and cases in which lenticular opacities and seizures antedated serum calcium abnormalities [7] certainly suggest that the natural history of this entity includes a phase of parathyroid activity sufficient to maintain a normal serum calcium level at a time when an underlying abnormal process of calcium metabolism produces ectopic calcification and seizures. The few biopsy cases of pseudohypoparathyroidism in which parathyroid hyperplasia has been found, and the case of Palubinskas and Davies in which spontaneous reversion to a normocalcemic state occurred in a previously hypocalcemic patient, suggest varying degrees of compensatory ability of the parathyroid glands. In the latter case, although parathyroid activity was sufficient to maintain a normal serum calcium level, the development of calcification of the basal ganglia during the normocalcemic phase suggests a continuing abnormality of calcium metabolism not under parathyroid control. After observing the family reported in this study, it is tempting to speculate that the involved members represent examples of varying stages of the natural history of an inherited defect of calcium metabolism resulting in ectopic calcification only (Case XI), ectopic calcification with parathyroid overactivity and normocalcemia (Case VI), ectopic calcification with parathyroid overactivity insufficient to maintain normocalcemia (Cases I, II, IV, V, VII and IX), and ectopic calcification with ultimate parathyroid atrophy (Case XIII). Whether the basic genetic defect lies in a derangement of the equilibrium between calcium in bone and extracellular fluid, and hence under parathyroid control, or in a qualitative change in the calcium-binding properties of the serum proteins and calcium transport mechanisms is unknown.

This case study suggests that the present classification of syndromes of abnormal calcification in terms of the state of parathyroid glands and measurements of serum total calcium requires critical review.

SUMMARY

A syndrome of calcification of the basal ganglia and hypocalcemia not conforming to any specific diagnostic pattern was found in three generations of the same family. One subject presented symptoms and signs similar to those of idiopathic hypoparathyroidism, two had familial calcification of the basal ganglia without serum calcium abnormalities, six presented a clinical picture suggestive but not diagnostic of pseudohypoparathyroidism.

The relationship of this syndrome to other states of familial ectopic calcification with or without hypocalcemia is discussed.

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Familial Systemic Lupus Erythematosus*

A Review of the Literature, with a Report of Ten Additional Cases in Four Families

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THE first report of overt systemic lupus erythematosus (SLE) in close relatives was published in 1951 [*1*]. In a review of the literature we have been able to find reports of fourteen families in which close relatives have SLE [*1–14*]; in addition, we have learned of two other families which have not been reported [*15,16*]. The findings in these fourteen previously recorded families and the two additional unreported families are summarized in Table I. McKusick [*17*] in a review of genetic factors in diseases of connective tissue, has included an extensive review of familial SLE, including eight of the families listed in Table I.

Sequeira [*18*] in 1903 reported two families, each with two sisters who had discoid lupus erythematosus. This report preceded the reports of familial SLE. McCuistion and Schoch [*19*] described possible discoid lupus erythematosus in a male infant whose mother subsequently had SLE. Zeisler and Bluefarb [*20*] observed a brother and sister with discoid lupus erythematosus and thyrotoxicosis whose mother, father and two sisters also had thyrotoxicosis. Beckett and Lewis [*21*] recently described a family in which the daughter had discoid lupus erythematosus; nine years later SLE developed in the mother. Both of these patients had hypergammaglobulinemia. The presence of systemic manifestations in patients with "discoid" lupus has been reported [*22*].

The present report is concerned only with families in which at least two members have SLE, with typical clinical findings and positive L.E. cell preparations, or typical findings at autopsy. Ten cases of familial SLE occurring in four families are recorded. Data on these families are briefly summarized in Table II.

CASE REPORTS

Family A

CASE I. A thirty-two year old Mexican housewife (A. A.) was referred to the Harbor General Hospital in August 1951. She had had fever, chills and joint pain since April 1951 and also recent onset of chest pain. She had been treated by her private physician for "rheumatism" with salicylates, penicillin and bed rest. On physical examination, she was acutely ill, showing flushed facies, distended neck veins, a macular facial and anterior trunk eruption, and a grade 1 systolic murmur at the base of the heart. Her liver was slightly enlarged but not tender. The left ankle joint and both knees were tender. The laboratory work-up on admission included a hemoglobin of 8.6 gm. per cent and a white cell count of 7,500 per cu. mm. Her electrocardiogram showed tachycardia and low voltage. After three months of hospitalization she was discharged on a regimen of prophylactic sulfonamides, with a diagnosis of rheumatic fever. She was readmitted on April 5, 1952, with respiratory difficulty, skin rash, chills and a history of recurrent fever since the previous discharge from the hospital. A chest roentgenogram taken on admission revealed extensive bilateral parenchymal infiltration. She died suddenly on April 17, 1952, after apparent improvement in her clinical condition. At autopsy, she was found to have focal interstitial myocarditis, pericardial effusion, confluent pneumonia with acute tracheobronchial lymphadenitis, generalized chronic lymphadenitis, and focal interstitial nephritis with glomerulonephritis. The autopsy diagnosis was disseminated lupus erythematosus.

CASE II. A fourteen year old Mexican girl (B. A.), daughter of A. A. (Case I), was first seen by her private

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TABLE I

REPORTS OF FAMILIAL DISSEMINATED LUPUS ERYTHEMATOSUS

Investigator	Sex and Age (yr.) at Onset	Relationship	Died	Autopsy	Remarks
Davis, Gutridge [1]	F,18	Identical twins	Yes	No	Diabetes mellitus and SLE
	F,20	Identical twins	Yes	Yes	SLE
Tikhonov-Bugrov [2]	M,15	Brother	Yes	Yes	Miliary tuberculosis and SLE
	F,18	Sister	Yes	Yes	SLE
Pirofsky, Shearn [3]	F,34	Mother	Yes	Yes	Miliary tuberculosis and SLE
	M,17	Son	Yes	Yes	SLE
Adams [4]	F,39	Mother	Yes	Yes	Autopsy diagnosis in retrospect
	F,27	Daughter	No	...	SLE
Willis [5]	F,10	Sister	Yes	No?	Typical course, died
	F,20	Sister	Yes	Yes	SLE
	F,19	Sister	Yes	Yes	SLE, 2 of 3 other sisters may have mild SLE
Glagov, Gechman [6]	F,39	Mother	Yes	No	SLE
	F,18	Daughter	Yes	Yes	SLE
Agranat, Bersohn, Lewis [7]	F,22	Sister	No	...	SLE
	F,39	Sister	No	...	"Rheumatoid" but L.E. preparation positive
Leonhardt [8]	F,43	Sister	Yes	Yes	SLE
	F,21	Heterologous twin	Yes	Yes	SLE
	F,17	Heterologous twin	No	...	Clinical (L.E. preparation negative); a sister has essential hypergammaglobulinemia
Wagenhals, Burgeson [9]	F,22	Identical twins	Yes	No	SLE
	F,26	Idenitcal twins	Yes	No	SLE
Bloom [10]	F,27	Sister	No	...	SLE, no details, very brief description
	F,22	Sister	Yes	?	SLE
Losada [11]	F,18?	Mother	No	...	SLE
	F,10	Daughter	No	...	SLE
Griffin, Ulloa, Holley [12]	M,43	Father	No	...	SLE
	F,26	Daughter	Yes	No	SLE, her brother who died at age 15 may have had SLE
Dias, Farina, Prata [13]	F,24	Mother	No	...	SLE
	F, Premature infant	Daughter	Yes	No	SLE
Larsson, Leonhardt [14]	F,30	Sister	Yes	Yes	SLE
	F,24	Sister	No	...	Twin sister has hypergammaglobulinemia, another sister has rheumatoid arthritis
Dubois [15]	F,41	Mother	Yes	Yes	SLE
	F,20	Daughter	No	...	SLE
Dubois [16]	F,—	Father's sister	Yes	No	SLE
	F,15	Niece	No	...	SLE, father died of "rheumatoid arthritis and periarteritis

physician in April 1957. She complained of anorexia, weight loss and easy fatigability, and was found to be anemic and to have albuminuria. Over a two month period vague abdominal pains, an erythematous facial eruption and migratory arthritis developed. She was hospitalized in the Harbor General Hospital in June 1957. A diagnosis of disseminated lupus erythematosus was confirmed by positive L.E. cell preparations. She responded well to treatment with steroids, and was discharged after a short period on a regimen of chloroquine and steroids, and did well. In July 1958, she discontinued her medications and suffered a severe sunburn over the face and extremities. Three days later she became symptomatic with fever, pleuritic pain and abdominal cramping. These symptoms progressed, and on July 13, 1958, she was readmitted to the Harbor General Hospital. The findings included a pleural effusion, a maculopapular erythematous eruption on the face, and generalized edema. She was anemic and had albuminuria and

TABLE II

ORGAN INVOLVEMENT AND OUTCOME

Case	Patient	Sex and Age (yr.) at Onset	Relationship	Died	Autopsy	Organs or Systems Involved					
						Skin	Musculo-skeletal	Kidney	Heart	Lungs	Central Nervous System
					Family A						
II	A. A.	F,32	Mother	Yes	Yes	X	X	X	X	X	...
	B. A.	F,14	Daughter	No	...	X	X	X	...	X	...
					Family B						
III	A. B.	M,36	Brother	Yes	No	...	X	X	X	X	X
IV	B. B.	M,18	Brother	No	...	...	X	...	X	...	...
					Family C						
V	C. C.	F,26	Sister	No	...	...	X	...	...	...	...
VI	G. C.	F,14	Sister	No	...	X	X	X	...	X	...
VII	H. C.	F,10	Sister	Yes	Yes	X	X	X	...	X	...
VIII	I. C.	F,11	Sister	No	...	X	X	...	...	...	...
					Family D						
IX	A. D.	F,14	Sister	Yes	Yes	X	X	X	X	X	X
X	B. D.	F,22	Sister	No	...	...	...	...	...	...	..

hemoglobinuria. Her serum globulins were increased, and her L.E. preparations were positive. She was treated with large doses of hydrocortisone, given intravenously, and bed rest, and has done well since August 1958 on a regimen of steroids and chloroquine.

Family B

CASE III. A thirty-six year old Mexican man (A. B.) was admitted to the Los Angeles County Hospital on September 26, 1955. Pain in his legs, arms and chest had been present for four months; swelling of his face, eyes, legs and abdomen for three weeks. He had recently lost 20 pounds. His past history was noncontributory except for recurrent asthma since 1945. On physical examination he appeared well developed and well nourished but somewhat lethargic. His blood pressure was 180/120 mm. Hg, pulse 105 and temperature 99°F. His face appeared edematous. Examination of his lungs and heart revealed no abnormalities. The axillary lymph nodes were enlarged. The liver was palpable 2½ fingerbreadths below the right costal margin, and his spleen was enlarged to percussion. Presacral edema and pitting edema of the legs were present. Laboratory work on admission included a hemoglobin of 11 gm. per cent and a white cell count of 14,400 per cu. mm. Albuminuria and hematuria were present. Pneumonia of the upper lobe of the right lung and cardiomegaly were seen on the chest roentgenogram. The electrocardiogram showed T wave changes. L.E. cell preparations were positive. His hospital course was progressively downhill, despite massive doses of steroids. On November 20, 1955, he had several convulsions, and on November 30 he died of uremia with a blood urea nitrogen of 226 mg. per cent, a potassium of 7.8 mEq. per L. and a CO_2 of 15 mEq. per L. Permission for autopsy could not be obtained.

CASE IV. An eighteen year old Mexican boy (B. B.), brother of A. B. (Case III), was first admitted to the Los Angeles County Hospital on January 5, 1956. He had had pain in the shoulders, knees and fingers for seven months and had been treated by his private physician for rheumatic fever. Chest pain had been present for three weeks, dyspnea for two days. On physical examination, he appeared well developed and well nourished, but acutely ill. The blood pressure was 132/80 mm. Hg, pulse 130, temperature 101°F. His respiratory excursion was limited, and rales were heard in the lower half of the left side of his chest.

The heart was not enlarged to percussion, but the tones were distant. After admission a pericardiocentesis was performed; on January 10, three days after the initial tap, a second attempt was unsuccessful. Three L.E. cell preparations were positive. The patient responded well to the administration of steroids, and was discharged on January 23, 1956. Since then he has remained asymptomatic on therapy, and at present is being treated with steroids and chloroquine.

Family C

CASE V. A twenty-six year old Negro housewife (C. C.) was first seen in the White Memorial Clinic on September 5, 1958. She had had a four month history of periodic swelling of the ankles and hands. No other joints were involved, and there was no associated fever or chills. She had had a brief episode of fever four months before admission, which was treated by her private physician with streptomycin. Another private physician diagnosed anemia and treated her with iron and vitamin B_{12}. The past history and system review was non-contributory. The patient appeared well developed but rather thin, and in no distress. The blood pressure was 110/60 mm. Hg, pulse 96, temperature 98.6°F., height 61½ inches, weight 88 pounds. The physical examination was within normal limits except for diffuse soft tissue swelling of the hands, feet and ankles. The other joints appeared normal. Her hemoglobin was 12.2 gm. per cent, the white cell count 4,800 per cu. mm. and the urinalysis normal. Several L.E. cell preparations were positive. She has been treated with aspirin, 10 gr. every 4 hours, and has remained asymptomatic to the present time.

CASE VI. A fourteen year old Negro girl (G. C.), sister of the preceding patient, was first admitted to the Los Angeles Childrens Hospital on June 7, 1955. Two weeks before admission fever, joint pains and some joint stiffness developed. The physical examination was within normal limits except for a coarse red rash over the left eye. Laboratory findings included a white cell count of 7,500 per cu. mm., albuminuria and microscopic hematuria and pyuria. The serum albumin : globulins were 3.5 : 3.4 gm. per cent; the serum gamma globulins by an immunologic method were 3 gm. per cent. A bone marrow L.E. cell preparation was positive. A chest roentgenogram showed left pleural effusion. She responded well to the administration of steroids and was discharged twenty days after admission. She was readmitted two months later because of a desquamating rash over her face and upper trunk, a left pleural effusion, and elbow pain. She again responded well to rest and steroid therapy and was discharged in four days. Three months later she had another exacerbation of her rash and left pleural effusion. She was discharged after a month and a half of hospitalization, and has continued to do quite well, remaining essentially asymptomatic. At present she is being treated with chloroquine.

CASE VII. A ten year old Negro girl (H. C.), sister of the preceding two patients, was first admitted to the Los Angeles Childrens Hospital on April 9, 1954. At that time she complained of fever, lethargy and pain in her ankles and feet. The L.E. cell preparation was positive. She had a "butterfly rash" across her face. She was followed up in the outpatient department and had a total of six admissions for exacerbations of her disease despite continuous steroid therapy. Her last admission was on April 10, 1956, when she entered with a history of cough and fever. She appeared acutely ill, with a Cushingoid appearance and a somewhat "blotchy" skin. The physical examination was otherwise non-contributory. While in the hospital she complained of abdominal pain, had one black stool, and was given an ulcer regimen. She had many skin infections, and hypertension developed. Her course was progressively downhill, and she died on July 10, 1956. At autopsy she had edema and pneumonia of the lungs, marked fatty vacuolization around the central veins of the liver, congestion and fibrosis of the spleen, atrophy of the adrenal cortex, and hyalin-fibrillar material at the basement membranes of the glomeruli of the kidney. There were multiple skin abscesses and small punctate hemorrhages of the gastrointestinal tract.

CASE VIII. An eleven year old Negro girl (I. C.), sister of the three patients just described, was admitted to the Los Angeles Childrens Hospital on March 29, 1958. She complained of fever, lassitude, anorexia, abdominal pain and migratory joint pains for two weeks. Four days before admission a butterfly rash developed on her face. Past history and system review were non-contributory. On physical examination she appeared well developed but thin. The blood pressure was 106/76 mm. Hg, pulse 140, and temperature 104.8°F. Her weight was 68 pounds. An erythematous butterfly rash was present on the face. The chest was clear, and the heart was not enlarged. The second pulmonic sound was greater than the aortic second sound, and a short grade 2 systolic murmur was heard along the left sternal border. Generalized adenopathy was present. No joint abnormalities were noted. Laboratory work on admission included a hemoglobin of 10.1 gm. per cent, a white cell count of 4,300 per cu. mm., and a urinalysis which showed a trace of albumin and microscopic pyuria. Blood and marrow L.E. cell preparations were positive. She was started on steroid therapy and made an uneventful recovery. She has since been followed up in the outpatient clinic and has remained asymptomatic on a regimen of steroids and chloroquine.

Family D

CASE IX. A fourteen year old Negro girl (A. D.) was admitted to St. Louis Childrens Hospital on July

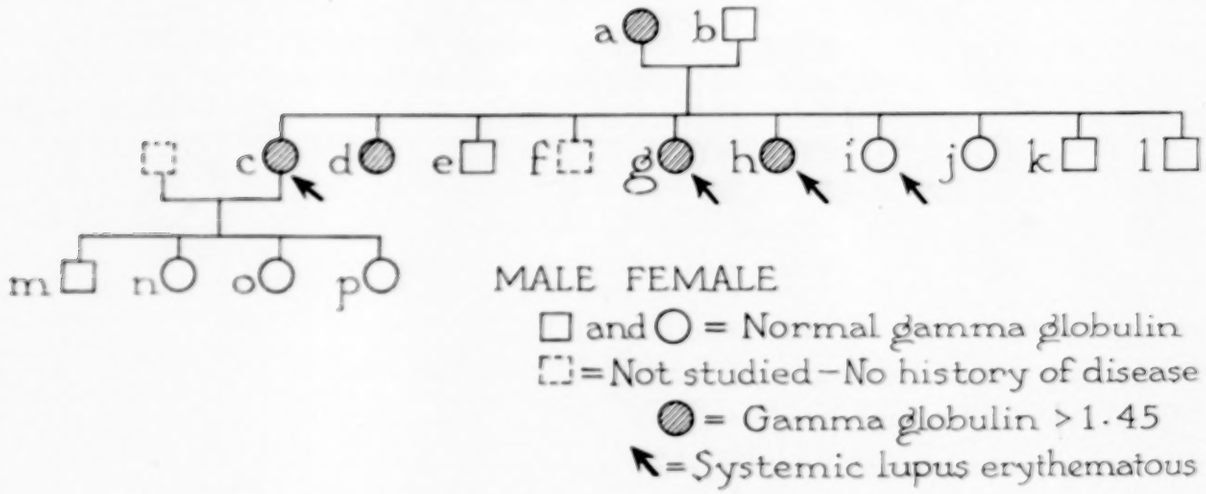

FIG. 1. Relationship of family C (c is Case V, g is Case VI, h is Case VII and i is Case VIII).

12, 1953. At that time she had a rash on her face, which had been present for six weeks, and some aching in her knees. Physical examination at that time was within normal limits, except for a desquamating rash over both cheeks with a "butterfly" distribution. Laboratory work included a hemoglobin of 14 gm. per cent, a white cell count of 2,650 per cu. mm. and a normal urinalysis. An L.E. cell preparation then was negative. She was discharged in five days, but a month later the rash spread over the face, elbows and palms. Cervical adenopathy and dark urine had also developed. Laboratory work included a white cell count of 3,300 per cu. mm. and a normal urinalysis. The serum albumin/globulins were 3.58/4.35 gm. per cent. An electrocardiogram revealed evidence of myocardial disease. On her fourth admission, in April 1954, she had a positive L.E. cell preparation, albuminuria, and microscopic hematuria and pyuria. Her course was progressively downhill, and she died on July 17, 1954 after a series of generalized convulsions. At autopsy she was found to have focal hyperpigmentation of skin of the face, upper thorax and arms, subacute glomerulonephritis with necrotizing arteriolitis (fibrinoid degeneration) of the kidneys, hypertrophy of the heart, fibrous pleural adhesions, fibrous thickening and adhesions of the pericardium, and fibrous peritoneal adhesions. Petechiae and ecchymoses of the endocardium, pericardium, epicardium, renal pelves, ureters, gastric mucosa and small intestinal serosa were noted. Focal atelectasis of the lungs with focal hemorrhages was also present.

CASE X. A twenty-two year old Negro woman (B. D.), sister of the preceding patient, had an uneventful delivery of a normal male infant on September 28, 1957, at the White Memorial Hospital. In December 1958 she was seen in the Prenatal Clinic at the White Memorial Clinic because of anemia, gingivitis, weakness and adenopathy. She gave a history of gingival bleeding for three years. She had had a productive cough and blood-streaked sputum from 1952 to 1954, but physical examination and chest films in 1954 were within normal limits. In December 1958 her blood pressure was 110/40 mm. Hg and she had tender slightly bleeding gums, marked cervical adenopathy, and a spleen which was palpable 1 finger-breadth below the left costal margin. The laboratory work included a hemoglobin of 10.4 gm. per cent, a white cell count of 5,200 per cu. mm., a normal serum iron and serum iron-binding capacity, and a positive L.E. cell preparation. The serum total protein was 7.1 gm. per cent; electrophoresis showed an albumin of 53.5 per cent, an alpha-1 globulin of 4.5 per cent, alpha-2 globulin of 8 per cent, beta globulin of 9.6 per cent, and a gamma globulin of 24.4 per cent. On July 15, 1959, she delivered an 8 pound 6 ounce male infant. She received 2 units of packed red cells at the time of her delivery, and her postpartum course was essentially normal.

STUDY OF FAMILY C

The family relationship of family C is shown in Figure 1. Twelve asymptomatic members were interviewed, and physical examinations and laboratory studies were obtained in eleven of them in September and October of 1958. The laboratory work consisted of a hemoglobin, white cell count, stained differential, and routine urinalysis. In addition, L.E. cell preparation, total proteins by the biuret method, and paper serum electrophoresis with the Spinco "B" apparatus were obtained; the results of the latter tests are summarized in Table III. Those studied were the mother and father of the four patients, two sisters, and three brothers. A fourth brother would not consent to physical or laboratory

TABLE III

PROTEIN STUDIES IN FAMILY C

Subject	Relationship (to C. C.)	Age (yr.) and Sex	Clinical SLE	L.E. Preparation	Serum Total Proteins (gm. %)	Serum Electrophoresis					
						Albumin (%)	Globulins				
							Alpha-1 (%)	Alpha-2 (%)	Beta (%)	Gamma (%)	Gamma (gm. %)
A. C.	Mother	47,F	...	...	7.4	52.8	3.5	7.2	12.7	23.8	1.76
B. C.	Father	49,M	...	...	6.5	61.5	4.7	7.8	11.2	14.8	0.96
C. C.	Patient	27,F	X	+	8.5	37.0	3.0	8.0	9.0	43.0	3.65
D. C.	Sister	24,F	...	...	7.5	58.5	4.6	8.6	8.3	20.0	1.50
E. C.	Brother	22,M	...	...	8.1	64.8	3.2	7.9	9.3	14.8	1.20
F. C.	Brother	19,M	...	...	...	...	...	...	...	...	...
G. C.	Sister	18,F	X	+	7.1	61.5	3.4	9.8	10.4	14.9	1.06 (3.0*)
H. C.	Sister	11,F†	X	+	5.5	...	...	...	...	...	(4.0*)
I. C.	Sister	12,F	X	+	7.6	62.3	3.6	10.1	11.0	13.0	0.99
J. C.	Sister	11,F	...	...	6.7	55.5	6.8	10.2	13.6	13.9	0.93
K. C.	Brother	9,M	...	...	6.6	53.4	5.1	10.6	17.0	13.9	0.92
L. C.	Brother	4,M	...	...	7.0	67.1	4.1	6.7	9.7	12.4	0.87
M. C.	Son	11,M	...	...	6.6	63.1	5.2	8.1	8.8	14.8	0.98
N. C.	Daughter	9,F	...	...	6.9	60.5	4.3	7.5	8.4	19.3	1.33
O. C.	Daughter	8,F	...	...	7.4	59.3	5.3	9.2	7.3	18.9	1.40
P. C.	Daughter	7,F	...	...	6.8	61.9	5.2	9.0	9.4	14.5	0.99
					(6.2–8.0)	(58–75)	(2–4)	(4–8)	(7–12)	(9–21)	‡

NOTE: Figures in parentheses represent the normal range.

* By immunochemical method.

† Died in 1956 at the age of eleven.

‡ Mean 0.90 gm. per cent.
Mean plus 2 standard deviations is 1.45 gm. per cent.

examination, but gave no history of disease. Also studied were the son and three daughters of C. C. (Case v).

A. C., a forty-seven year old Negro woman, and mother of the four sisters with SLE, had no history of illness or other abnormalities except for two miscarriages. Her physical examination was within normal limits and her routine laboratory work revealed no abnormalities except for a hemoglobin of 10.6 gm. per cent.

B. C., father of the four patients with SLE, is a forty-nine year old Negro man whose medical history, physical examination and routine laboratory studies were within normal limits except for the presence of microscopic hematuria with 5 to 10 red cells per high power field.

D. C., a twenty-four year old Negro woman, sister of the patients with SLE, had a negative history except for the removal of an ovarian cyst in January 1958. Her physical examination and routine laboratory work revealed no abnormalities.

E. C., a twenty-two year old Negro man, and brother of the patients with SLE, had a normal history and physical examination, and normal routine laboratory findings.

F. C., a nineteen year old Negro boy, brother of the four patients with SLE, had a negative history, but would not consent to physical examination or laboratory study.

J. C., an eleven year old Negro girl, sister of the four patients with SLE, had a negative history and physical examination. Also her routine laboratory studies gave normal results. However, in December 1958, she had some aching in her wrist and fingers and a swollen left little finger, following a disease which may have been rubella. She was not seen at this time, and remained asymptomatic until March 1960 when she complained of knee pains. Laboratory studies were repeated then, the results of which were all within normal limits.

K. C., a nine year old Negro boy, brother of the four patients with SLE, had a negative history, physical examination and routine laboratory work. The hemoglobin was 11.8 gm. per cent.

L. C., a four year old Negro boy, brother of the four patients with SLE, had a negative history and physical examination. The laboratory work gave normal results except for a hemoglobin of 9.4 gm. per cent.

M. C., an eleven year old Negro boy and son of C. C. (Case v), had a negative history and a physical examination which revealed no abnormalities except for a few postcervical lymph nodes and a small umbilical hernia. Results of routine laboratory studies were normal.

N. C., a nine year old Negro girl, daughter of C. C., had a negative history. On physical examination, she had large tonsils. Results of routine laboratory studies were normal.

O. C., an eight year old Negro girl, daughter of C. C., had a negative history and physical examination except for enlarged tonsils. Results of routine laboratory work were normal.

P. C., a seven year old Negro girl, daughter of C. C., had a negative history and physical examination. Results of routine laboratory studies were normal except for microscopic hematuria, with 40 to 50 red cells per high power field.

COMMENTS

The occurrence of two cases of lupus erythematosus in the same family could be due to chance, but the number of such cases now reported makes it probable that this is more than just a chance occurrence. Also, the occurrence of three cases in one family, as described by Leonhardt, and in four sisters as in family C, argues against chance as the cause. These figures apply only to the overt disease.

The familial occurrence of SLE does not necessarily mean that it is on a genetic basis. Harvey et al. [*23*] in their review of lupus erythematosus mentioned various possible etiologic causes. Of those mentioned, the tubercular, streptococcal or viral etiology could be familial without being on a genetic basis. In cases in which a mother and child, or several siblings are involved, the disease could conceivably be transmitted through the placenta. It has been shown that the L.E. factor may be transmitted through the placenta [*24*]. A familial incidence of SLE might have its basis in the immunologic interrelationships of mother and fetus [*17*]. Placental transfer would not account for those cases in which the father may have been the carrier [*12,16*]. However, the father-child familial cases are rare and may be due to chance.

Leonhardt [*8,14*] has made extensive studies of asymptomatic relatives in two families with familial lupus erythematosus and has demonstrated that these families have hereditary hypergammaglobulinemia. He believes that familial SLE, at least in his patients, is a manifestation of an underlying genetically determined tendency to overproduction of gamma globulin. His study has shown that the siblings and children of his patients with lupus erythematosus have higher mean gamma globulin values than control subjects living under the same environmental conditions. The number of asymptomatic relatives that we have studied is not sufficient to confirm this. However, the mother and a sister of our patients did have moderately elevated gamma globulin levels. Also, not all of our patients with SLE had high gamma globulin levels. In H. C. (Case VII), who died, no electrophoretic studies were made, and in G. C. and I. C. (Cases VI and VIII) results of electrophoretic studies were normal but they were asymptomatic at the time this examination was made. G. C. (Case VI) had an elevated gamma globulin level by an immunologic method at an earlier date. C. C. (Case V) had an elevated gamma globulin level. The gamma globulin in SLE may be labile. In one of Leonhardt's patients, sibling number 10, the gamma globulin level decreased from 4.41 to 2.93 gm. per cent in a period of a little over one year. Eight of the ten cases reported here occurred in females. The occurrence of SLE in four sisters or in two brothers has not been previously reported.

SUMMARY AND CONCLUSIONS

The literature on familial SLE is reviewed and summarized in tabular form.

Ten additional cases in four families are reported. Eleven asymptomatic relatives of four sisters with familial SLE have been studied. The mother of these patients and a sister had moderately elevated serum gamma globulin levels.

Including these four families, we know of forty-four cases in twenty families. Whether the mechanism of this familial association is genetic and sex-linked remains to be determined. The association of SLE with familial hypergammaglobulinemia, as described by Leonhardt, is of interest. Our studies on this point are not conclusive, but are consistent with Leonhardt's hypothesis.

Acknowledgment: We are indebted to Dr. Alexis F. Hartmann, Head of the Department of Pediatrics, Washington University School of Medicine, for permission to include Case IX.

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Pseudoxanthoma Elasticum and Angioid Streaks*

A Review of 106 Cases

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Pseudoxanthoma elasticum is a dermatologic condition characterized by changes in the elastic tissue of the skin. Frequently, so-called angioid streaks are noted in the fundus of the eye, and this association of dermatologic and ophthalmologic findings has been termed the "Grönblad-Strandberg syndrome." Other important clinical manifestations that attest to the systemic nature of the disease are those that are secondary to degenerative arteriopathy.

The disease has been the subject of a recent comprehensive review by McKusick [*1*]. Although admitting to the inadequacies of the term, he referred to the entire syndrome as pseudoxanthoma elasticum.

Evidence that pseudoxanthoma elasticum is basically an abnormality of collagen tissue has been presented [*2,3*], but more recent studies have strongly supported the conventional view that it is a degenerative disease of elastic tissue [*4,5*]. The syndrome is inherited apparently as either a recessive or an irregularly dominant trait, but no clinical differences have been detected between the two genotypes. It has been said to be partially sex-limited to the female. That it is an uncommon disorder is indicated by the fact that prior to 1940 only 125 cases of cutaneous and ocular changes, and sixty-eight of cutaneous changes alone were described [*6*].

In an effort to shed additional light on the clinical and pathologic manifestations of this disorder we have reviewed the case records of 106 patients with pseudoxanthoma elasticum, angioid streaks, or both, seen at the Mayo Clinic from 1931 through 1958. In some of our cases skin and other surgically excised specimens of various tissues were available for microscopic study. In the latter, special attention was devoted to possible pathologic changes in the arteries.

RESULTS

Of the 106 patients whose records were reviewed, seventy-four had the typical cutaneous changes of pseudoxanthoma elasticum. Sixty-three of these seventy-four patients (85 per cent) also had angioid streaks in the ocular fundi; eleven had normal eyes. Ninety-five patients had angioid streaks in the ocular fundi. Sixty-three of these patients (66 per cent) had associated pseudoxanthoma elasticum but thirty-two (34 per cent) had no cutaneous manifestations. Two patients in the last group had associated osteitis deformans. (Table 1.) These percentages

Table 1
DIAGNOSIS AND SEX DISTRIBUTION OF PATIENTS IN PRESENT SERIES

Diagnosis	Females	Males	Total
Pseudoxanthoma elasticum			
Alone	10	1	11
With angioid streaks (Grönblad-Strandberg syndrome)	31	32	63
Angioid streaks			
Alone	10	20	30
With osteitis deformans	0	2	2
Total	51	55	106

* From the Sections of Medicine, Dermatology, Ophthalmology and Pathologic Anatomy, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

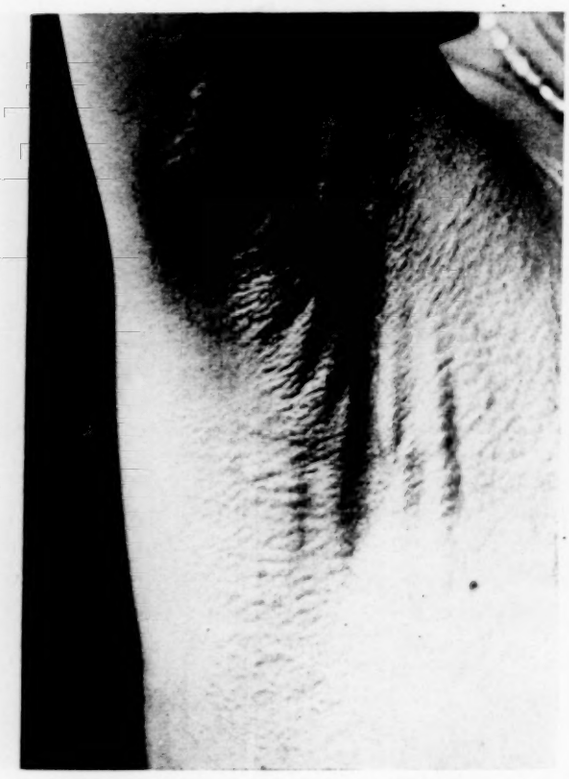

FIG. 1. Showing the typical lesions of pseudoxanthoma elasticum, consisting of chamois- to fawn-colored, slightly elevated papules arranged in streaks that tend to follow the linear markings of the skin. This is a patient's right axilla.

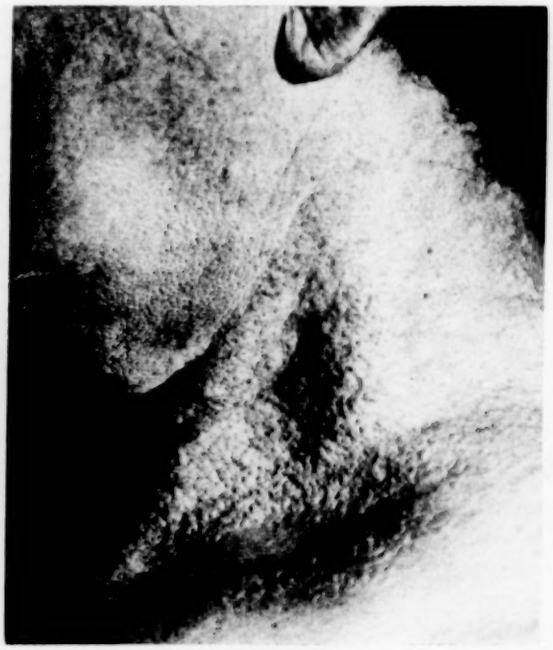

FIG. 2. Showing how the changes of the elastic tissue in the skin at times may be so far advanced that the skin loses its resiliency and, in this relaxed condition, resembles the plucked skin of a chicken.

are in general agreement with those in the collected series of Goedbloed [7] and Scholz [8]. Since not all our patients with angioid streaks were referred to the Section of Dermatology, and not all of our patients with pseudoxanthoma elasticum were referred to the Section of Ophthalmology, it is possible that some patients had subtle cutaneous or ocular changes that were not detected.

Sex and Age Distribution. Of the seventy-four patients with a definite diagnosis of pseudoxanthoma elasticum, thirty-three were males and forty-one were females, a ratio of males to females of 1:1.2. This slight preponderance of women in our series probably does not signify a partial sex-limited inheritance to the female. Rather, it may indicate a greater concern of the female for the cosmetic appearance of the skin on the exposed portions of the body which prompts her to seek medical advice. In this regard, it is interesting that among the group of thirty-two patients with angioid streaks but no cutaneous changes there were twenty-two males and ten females, a ratio of 2.2:1.

The ages of the patients at the time the diagnosis was initially made at the clinic ranged from ten to sixty-eight years, with an average age of forty-two years. More than 70 per cent of the diagnoses were made during the fourth and fifth decades of life. Of thirty-one patients with an adequate family history, only ten were aware of a similar disease in other members of the family.

Cutaneous Findings. The gross lesions of pseudoxanthoma elasticum are typically distributed in the intertriginous areas of the body, that is, in the folds of the skin at the sides of the neck, the flexural regions of the extremities, the axillae, the cubital and popliteal fossae, and in the creases of the groin, umbilicus and mammae. Early, small, chamois-colored papules are distributed in a linear arrangement along the body folds. At times it may be necessary to stretch the skin in these regions to accentuate the early lesions. The diagnosis may be made with ease when slightly elevated, fawn-colored papules are present in a linear and reticulated pattern. (Fig. 1.) If involvement is severe, the skin becomes distended, relaxed and sacculated. At this stage the affected skin has been likened to the skin of a plucked chicken. (Fig. 2.) While in most instances the diagnosis of pseudoxan-

thoma elasticum can be made clinically without biopsy of the skin, the cutaneous changes in some patients may be so early as to preclude a clinical diagnosis, and biopsy specimens of skin may be needed.

The histopathologic changes of pseudoxanthoma elasticum are pathognomonic. Sections stained with hematoxylin and eosin are almost always all that is needed for making the diagnosis, but the interpretation of minimal changes is facilitated by use of elastic tissue stains. The basic pathologic alteration is in the elastic tissue of the middle and lower thirds of the dermis. Changes in the epidermis and upper third of the dermis are not present; their absence adds substance to a definite diagnosis of pseudoxanthoma elasticum. A section of skin stained with hematoxylin and eosin will show an essentially normal epidermis and upper part of the corium, for the collagen will take the usual pink color of the eosin dye. In the middle and lower thirds of the corium, however, a peculiar distortion, fragmentation and rearrangement of the collagen bundles are evident. These portions of the corium have an altered reaction to the stain and show scattered whorls and tightly curled nests of somewhat basophilic material. An elastic tissue stain demonstrates that these changes are accounted for by alterations of the elastic tissue. The elastic fibers are curled on themselves, markedly shortened, and wound into small, tight balls. von Kossa's stain may disclose deposits of calcium in the involved portions of the dermis. If present, it is deposited about the individual elastic tissue bundles but not in the vessels of the skin.

Specimens of affected skin were available for study in twenty-one of the seventy-four cases of pseudoxanthoma elasticum reviewed in this study. The biopsy material was derived almost equally from male and female patients, that is, from twelve males and nine females. Sections of skin stained with hematoxylin and eosin were available for study in all twenty-one cases. Frequently, sections prepared with the van Gieson, the elast n H or the orcein stains for collagen and elastic tissues were also available. Some biopsy specimens were studied with special stains for calcium (von Kossa) and for iron (Prussian blue). All these slides were reviewed in detail and examined for possible changes in the small blood vessels of the skin.

The diagnosis of pseudoxanthoma elasticum could be made from the sections stained with hematoxylin and eosin alone in seventeen of the twenty-one cases in which a biopsy specimen of the affected skin had been obtained. The diagnosis also was confirmed by use of the elastic tissue stains in these seventeen patients. A definitive diagnosis was impossible in four cases even though sections prepared with hematoxylin and eosin and special stains were examined.

No abnormalities were noted in the dermal vessels in any of the sections. There was no degeneration or proliferation of elastic tissue in the intima of the small arteries of the skin even when the elastic tissue of the skin showed dystrophic changes. Stains for calcium were employed in six cases, in all of which deposits of calcium were present throughout the deranged elastic tissue in the corium. No iron was deposited in or around the small blood vessels of the skin.

The onset and the duration of the cutaneous changes of pseudoxanthoma elasticum in our series were variable. One girl in whom a positive diagnosis was made after biopsy at the age of ten years had had abnormal skin since the age of two years. The women in this series had been aware of their abnormal skin for an average of twenty years. Only three of the men knew the duration of their cutaneous changes: two of them presumed these abnormalities had always been present; one had been aware of them for about twenty-five years. This difference in awareness of the cutaneous changes is probably related to the concern of the female, and the lack of concern of the male, for the appearance of the skin on the exposed parts of the body.

Ocular Findings. Angioid streaks are cracks in the lamina vitrea (Bruch's membrane) of the eye; they are caused by degenerative changes in the elastic tissue composing this structure [*9*]. Their association with pseudoxanthoma elasticum was first pointed out by Grönblad in 1929 [*10*].

The ophthalmoscopic appearance is characterized by a network of streaks which lie behind the retinal vessels, resemble branching blood vessels, vary in color from dark brown to red, and are most numerous near the margins of the optic disks. Sometimes a ring of streaks surrounds the disk and gives the appearance of a cracked eggshell; from this ring additional streaks extend toward the periphery. Some streaks may be three or four times as wide as a retinal vein, and some may be very narrow. Their course is irregular. Often there is white

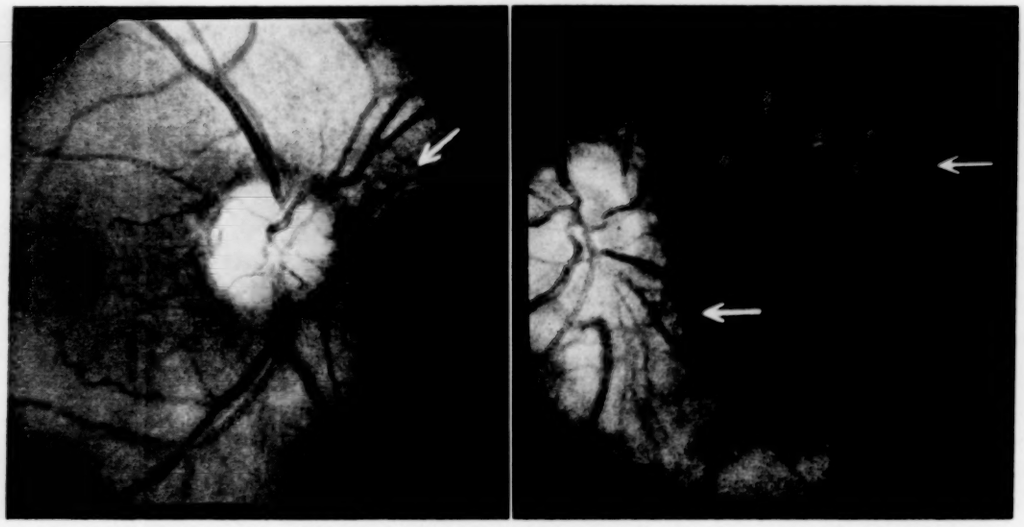

FIG. 3. Ocular fundus. *Left*, arrow indicates an early angioid streak of the right eye. There were no visual symptoms. *Right*, lower arrow points to a large angioid streak of the right eye. The upper arrow indicates a chorioretinal scar caused by hemorrhage (below) from streak (above). This patient had loss of central vision in both eyes.

proliferative connective tissue on or near the streaks. Commonly there are numerous white dots at the level of Bruch's membrane. About a third of the affected patients have hemorrhages along one or more of the fissures; these lesions are ordinarily asymptomatic unless the hemorrhage extends into the macula. (Fig. 3.) Angioid streaks are nearly always bilateral, although usually asymmetric in the two eyes. The lesions may progress slowly or they may remain stationary for years. Trauma to the eye apparently can cause progression of the lesion in the same way that pressure on a cracked egg causes further damage to the egg.

If the maculas are affected, as they are eventually in the majority of cases, an exudative mass of hemorrhage and edema may destroy them, leaving a discoid patch of fibrous tissue and a large permanent central scotoma in the affected eye. Extension of the hemorrhage into the vitreous seems to be extremely unusual, and total blindness therefore is very rare.

In our series, disturbed vision was the presenting complaint of most patients, that is, in forty-nine (66 per cent) of the seventy-four patients with pseudoxanthoma elasticum and in twenty-two (69 per cent) of the thirty-two patients with angioid streaks and no cutaneous changes. The discovery of angioid streaks in the remaining patients was incidental. Two patients had angioid streaks confined to one eye.

Defects in vision due to degenerative or hemorrhagic changes in the maculas were demonstrable in sixty-nine (73 per cent) of the ninety-five patients with angioid streaks. The visual loss progressed in the majority to bilateral loss of central vision to 20/200 or less. Macular degeneration was bilateral in all except eight of the sixty-nine patients. One patient sustained a hemorrhage into the vitreous, three had glaucoma, and two had unilateral detachment of the retina. The initial visual loss in four patients followed trauma to one eye. Both patients with osteitis deformans lost their central vision. The onset of macular involvement occurred at ages fourteen, eighteen and nineteen, respectively, in three patients, in the third decade in seven patients, in the fourth decade in fourteen patients, in the fifth decade in twenty-five patients, in the sixth decade in fifteen patients and from ages sixty-one to sixty-six in five patients. Usually the second eye was involved within a few days or weeks after the onset of difficulty in the first eye, but a few patients retained good vision in one eye for as long as eleven to eighteen years after the loss of central vision in the first eye.

Arterial Findings. Arterial disease associated with pseudoxanthoma elasticum or the Grönblad-Strandberg syndrome may be manifested clinically by roentgenologic evidence of premature calcification of the arteries of the extremities, diminution or absence of peripheral arterial pulsations, symptoms of peripheral or coronary arterial insufficiency, hypertension or hemor-

rhagic phenomena. Subarachnoid hemorrhage is said to be a common cause of death [*1*], and involvement of visceral arteries may produce severe gastrointestinal hemorrhage [*11*]. Calcification of peripheral arteries has been reported to occur as early as the ninth year of life [*12*]; it is sometimes extensive and perhaps represents calcium deposition in areas of elastic tissue degeneration in the arterial wall, similar to the calcium deposition in the corium. It is not clear from the reports in the literature whether the roentgenograms of the extremities show the medial type of diffuse, finely divided calcinosis or the atherosclerotic type of localized opaque clumps of calcium. Carlborg [*13*] expressed the view that the diminution or absence of peripheral arterial pulsations in this disease is not due to intraluminal occlusion but to degeneration and fragmentation of the elastic fibers in the arterial wall so that the patent artery is unable to transmit the pulse wave in a normal fashion. However, Scheie and Freeman [*14*] found at biopsy a marked reduction in the diameter of the lumen of an ulnar artery due to muscular hypertrophy, and other histologic studies have shown lesions indistinguishable from ordinary arteriosclerosis [*1*]. Woo and Chandler [*11*] demonstrated degeneration of the elastic tissue of arteries of the gastric wall; there was fragmentation of the internal lamella and the walls of some of the arteries showed thinning with formation of micro-aneurysms.

In only twelve (16 per cent) of our seventy-four patients with pseudoxanthoma elasticum were the peripheral arterial pulsations absent or greatly diminished clinically. Two of these twelve patients had intermittent claudication; none had peripheral arterial insufficiency severe enough to cause trophic changes or ischemic rest pain. The ages of these twelve patients ranged from sixteen to sixty-six years with a mean age of forty-two years. The mean age of this relatively small group of patients with pseudoxanthoma elasticum and clinical evidence of arterial disease is significantly less than the mean age of fifty-three years of a large group of non-diabetic patients with atherosclerotic occlusion of the femoral artery seen at the Mayo Clinic [*15*]. This suggests that some patients with pseudoxanthoma elasticum do have premature, chronic occlusive arterial disease. Only one (a seventy-eight year old woman) of the thirty-two patients with angioid streaks but no cutaneous involvement had clinically evident peripheral arterial occlusive disease. Typically in the affected patients the pulsations in one or more of the posterior tibial, dorsalis pedis, radial or ulnar arteries are not palpable or are greatly diminished in amplitude. Pulsations of the popliteal arteries were occasionally absent or diminished, but those of the femoral arteries in Scarpa's triangle were rarely abnormal.

A 16 per cent incidence of occlusive peripheral arterial disease associated with pseudoxanthoma elasticum is probably lower than the true incidence of peripheral arterial involvement in these patients. A minority of our patients underwent complete clinical evaluation in the Section of Internal Medicine, and it is probable that if all had had careful assessment of peripheral arterial pulsations, more patients with minor degrees of arterial insufficiency would have been detected. Of our patients with pseudoxanthoma elasticum who had a careful peripheral vascular examination, approximately 80 per cent had evidence of chronic occlusive peripheral arterial disease.

Angina pectoris was present in five of the patients with pseudoxanthoma elasticum but in none of the patients with angioid streaks alone; one with angina pectoris had had two previous myocardial infarctions. A cerebral vascular accident had affected five patients with pseudoxanthoma elasticum prior to our examination; another patient suffered from intermittent cerebral vascular insufficiency. Thus, excluding patients with more than one arterial system involved, nineteen of the seventy-four patients (26 per cent) had clinical evidence of peripheral, coronary or cerebral arterial disease. Although no control data are available for comparison, this incidence of arterial involvement appears to be higher than that ordinarily expected in a group of patients of comparable age and sex distribution. In addition to the cerebral vascular disease mentioned, three patients with pseudoxanthoma elasticum had epilepsy and one patient had myasthenia gravis. None of our patients with angioid streaks alone had coronary or cerebral arterial disease, and only one patient in this group had peripheral arterial disease.

Blood pressure recordings were available in thirty of the seventy-four patients with pseudoxanthoma elasticum. Hypertension, arbitrarily defined as a blood pressure of more than 150 mm. Hg systolic and 90 mm. Hg diastolic, was present in seven (23 per cent) of these patients. In a

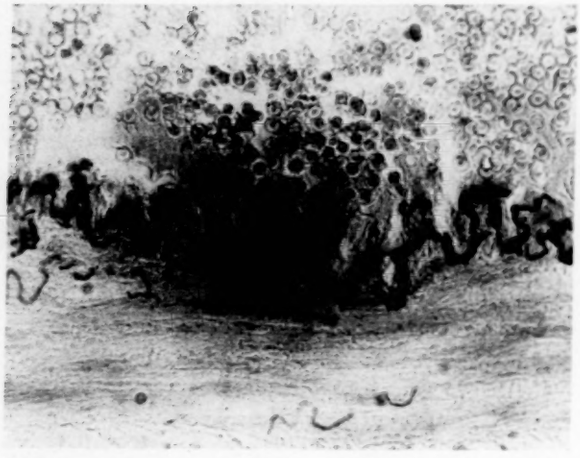

FIG. 4. Section of uterine artery (Prussian blue stain, original magnification × 450). The internal elastic lamina is fragmented. The dark areas represent deposits of iron.

previous Mayo Clinic group of 100 healthy men between the ages of forty and sixty years only 9 per cent were found to have blood pressures exceeding these limits [*16*]. Assuming these two groups of patients are comparable, the incidence of hypertension in patients with pseudoxanthoma elasticum is significantly higher than the incidence in normal persons.

Ten of the seventy-four patients with pseudoxanthoma elasticum (14 per cent) had gastrointestinal bleeding from one cause or another. Six of these had bleeding from the large bowel: three had chronic ulcerative colitis, and three had internal hemorrhoids as the cause of the bleeding which was not serious. The four remaining patients bled from the upper part of the gastrointestinal tract. One of these suffered from atrophic gastritis; another had a bleeding duodenal ulcer; a third had one episode of blood-tinged emesis for which no diagnosis was established; and the fourth (a sixteen year old boy) was surgically explored for repeated upper gastrointestinal bleeding, but no cause for the bleeding was found. Two of the thirty-two patients with angioid streaks alone had a history of bleeding from the upper part of the gastrointestinal tract. One of these had roentgenologic evidence of a duodenal ulcer for which a gastroenterostomy was performed. The other patient had roentgenologic evidence of esophageal varices and subsequently died elsewhere of massive hemorrhage at the age of thirty-one years.

Pathologic Aspects. An attempt was made to evaluate further any possible arterial disease in twelve patients by examining specimens of tissue removed during surgical procedures. Tissue was available from the thyroid in two cases, from the prostate in two cases, from hemorrhoids in two cases and from the spleen, uterus, gallbladder and tibia in one case each; small specimens of the liver and stomach were available in one case each. Sections were cut from the most vascular area available and stained with hematoxylin and eosin, van Gieson's stain for elastic tissue, von Kossa's stain for calcium and the Prussian blue for iron. In three cases sections of the larger branches of the splenic, thyroid and uterine arteries showed degeneration of the elastic tissue in the internal elastic lamina. The ages of the patients who had these changes were twenty-six, twenty-nine and sixty-five years. In these cases, sections stained with hematoxylin and eosin showed what appeared to be deposits of calcium in the areas of elastic tissue degeneration. However, von Kossa's stain failed to demonstrate calcium in these areas. The Prussian blue stain revealed that the areas previously suspected of containing calcium actually contained iron. (Fig. 4.) This finding, to our knowledge, has not been previously reported in cases of pseudoxanthoma elasticum.

Hass [*17*] commented on the affinity of elastic tissue, particularly injured elastic fibers, for calcium and iron. Hagedoorn [*18*] found iron in Bruch's membrane in a patient with angioid streaks; he stated that iron probably played a role in the process of angioid streaks. It is possible in our cases that the iron was originally deposited along with calcium but that the calcium was subsequently dissolved in the formalin fixative in which the tissues were stored. Microscopic examination of the tissue from the nine other patients showed no arterial abnormalities. It has already been mentioned that the dermal vessels showed no abnormalities.

SUMMARY

The records of 106 patients given the diagnosis of pseudoxanthoma elasticum, angioid streaks, or both (Grönblad-Strandberg syndrome) at the Mayo Clinic from 1931 through 1958 were reviewed. Seventy-four patients had pseudoxanthoma elasticum, and sixty-three of these seventy-four patients (85 per cent) had associated angioid streaks in the ocular fundi. Ninety-five patients had angioid streaks, and thirty-two of these patients (34 per cent) had no clinical evidence of associated pseudoxanthoma

elasticum; two patients with angioid streaks had associated osteitis deformans.

The greatest cause of morbidity in this series was loss of central vision which occurred in sixty-nine of the ninety-five patients (73 per cent) who had angioid streaks of the ocular fundi; forty-nine (51 per cent) of these patients experienced visual problems before the sixth decade of life. A small number of female patients with pseudoxanthoma elasticum complained of the unsightliness of the skin lesions. The characteristic clinical and histologic findings in the skin and the ophthalmoscopic findings are discussed.

Sixteen per cent of the seventy-four patients with pseudoxanthoma elasticum had clinical evidence of occlusive peripheral arterial disease at a younger mean age than would ordinarily be expected, and 26 per cent had clinical evidence of occlusive peripheral, coronary or cerebral arterial disease. The incidence of hypertension in these patients appears to be relatively high. Ten patients with pseudoxanthoma elasticum and two with angioid streaks alone had episodes of gastrointestinal bleeding, some of which were serious.

In three cases histologic examination of surgically excised tissue revealed degenerative changes of elastic tissue in the internal elastic lamina of certain arteries. Iron was present in the areas of elastic tissue degeneration, a finding which, to our knowledge, has not been previously reported in the arteries of patients with pseudoxanthoma elasticum.

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The Chromosomal Etiology of Congenital Gonadal Defects*

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WITHIN the past decade significant advances in the study of certain congenital gonadal defects have prepared the way for a unified concept of etiology, supported by basic genetic principles [*1*]. Impetus to the study of intersex was provided by Barr and Bertram [*2*] in 1949 with the discovery of a characteristic chromatin mass adjoining the inner surface of the nuclear membrane in the majority of cells of normal females (chromatin-positive pattern) [*3,4*]. In cells of normal males a smaller chromatin mass was infrequent or not present (chromatin-negative pattern) [*2–4*]. Clinically, the human tissues most commonly utilized for chromatin staining have been the skin [*4,5*], buccal mucosal scrapings [*6*], placental elements [*7,8*] and vaginal mucosa cells [*9*]. Improved technics of counting chromosomes have established that the normal human nucleus contains 46 chromosomes [*10–17*].‡ Twenty-two paired autosomes and a pair of sex chromosomes designated as XX in the normal female and XY in the normal male have been identified [*10*]. The origin of the chromatin mass of Barr is still uncertain. It was believed to represent the fused heterochromatic (deeply staining) regions of the two homologous X chromosomes by a majority of investigators [*3,11,19, 20a,20b*]. However, recent evidence suggests that the paternally derived X chromosome is heterochromatic and may form the chromatin mass in the absence of the maternally derived X chromosome [*21a,21b*]. The chromatin mass is not influenced by exogenous hormone administration or by an abnormal endogenous hormonal status, and is manifest in resting nuclei of human cells before gonadal development [*3,22*].

In approximately 2 to 6 per cent of the neutrophils found in normal females a characteristic nuclear lobule (drumstick) is noted which is rarely encountered in human males [*3,20b,23*]. This lobule is not identical with the sex chromatin and should not be utilized as a marker of genetic content [*20b,24,25*].

Normally, the spermatozoan and the ovum each contribute 23 chromosomes to produce a zygote of 46 chromosomes [*26*]. If the zygote contains two X sex chromosomes, ovaries develop from the fetal gonadal cortex. If a spermatozoan containing a Y chromosome fertilizes an ovum containing an X chromosome, testes develop from the fetal gonadal medulla. The developing medulla of the fetal testis is believed to secrete an androgenic substance which causes Wolffian duct development (epididymis, vas deferens and seminal vesicles) with regression of Müllerian duct elements (the primordia of fallopian tubes, uterus and vagina) [*5,22,27*]. This testicular hormone (which is not identical with the adult testicular hormone) apparently travels locally, affecting the entire accessory genital tract including the external genitalia [*5,27*].

The classic experiments of Jost [*22*] established the relationship of this androgenic hormone to the physical appearance of the fetus. If rabbit embryos have their immature gonads removed before a crucial stage of differentiation, all will develop into agonadal animals with the outward anatomic appearance (phenotype) of a female and possessing female sex ducts. The human counterpart is the patient with Turner's syn-

‡ Kodani [*18*] has described some individuals (all Japanese except for one Caucasian) with 47 or 48 chromosomes, including one or two supernumerary chromosomes. This work has not been confirmed by others [*10,16*].

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drome [*28*] (*vide infra*). Furthermore, if the fetal testis is removed from a developing embryo and transplanted into an embryo castrated before duct differentiation, the accessory sex ducts around the transplant will differentiate into male structures [*5,22,27*]. In man, an analogous condition is found in those persons with true lateral hermaphroditism, in whom male internal sexual structures develop only on the side which has the testis [*5*] (*vide infra*). Three stages are involved in the development of the "anatomic sex" of an individual: (1) Chromosomal sex—the initial combination of sex chromosomes in the zygote which alters the corticomedullary balance of the fetal gonad in favor of cortical development (ovaries) or medullary development (testes). (2) Gonadal sex—ovaries or testes. (3) Phenotypic sex—the anatomic appearance of internal and external sex structures.

BASIC GENETIC PRINCIPLES

Most fundamental characters are probably under the control of a large number of genes (genetic balance). Three main classes of genetic change are recognized which may give rise to aberrant phenotypes [*29–31*].

I. Changes in Chromosome Number as Detected in Careful Chromosome Counts. Prior to formation of the zygote, the primary spermatocyte and primary oocyte, each containing 46 chromosomes, undergo two meiotic divisions to produce four nuclei, each with a haploid number of 23 chromosomes. In non-disjunction, a pair of homologous chromosomes do not separate so that both chromosomes go to the same nucleus, while the other is lacking the chromosome in question. The recent observations of abnormal chromosome counts in Turner's syndrome (45 chromosomes-XO) [*12,15a,15b,32–35*], XXX females (47 chromosomes) [*25,32*] and Klinefelter's syndrome (47 chromosomes-XXY) [*12,36–39*] suggest that non-disjunction involving the sex chromosomes occurred during maturation division [*15a,15b*]. It has been noted that in man the X and Y chromosome are frequently unpaired during metaphase of primary spermatocytes [*13*]. Both chromosomes could migrate to the same pole and thus produce non-disjunction resulting in a sperm that possesses both an X and Y chromosome or one that contains no sex chromosome. Likewise, an ovum or a polar body may be produced, one of which may contain an XX combination and the other no sex chromosome (O) [*15a,15b*]. (In order to clarify which parent is dominating the X, the maternal donation will be designated as /X/, /XX/ or /O/ for the remainder of the paper.) Therefore, a patient with Klinefelter's syndrome, possessing an XXY chromosome constitution, could be produced by union of an ovum possessing two X chromosomes with a normal spermatozoan (/XX/Y) or a normal /X/ ovum with a non-disjunctive XY sperm (/X/XY). A patient with Turner's syndrome possessing an XO chromosome constitution, could be produced by union of a normal /X/ ovum with an O spermatozoan (/X/O) or an /O/ ovum with an X spermatozoan (/O/X). An XXX individual could be produced by the union of a normal X spermatozoan with a non-disjunctive /XX/ ovum.

II. Changes in the Arrangement of the Gene Loci in the Chromosome due to Breakage. (A) Deletion—in which a portion of a chromosome is lost. (B) Duplication—in which a portion of a chromosome is duplicated. (C) Inversion—in which a chromosome segment is rotated by 180 degrees. (D) Translocation—in which the broken portion of the chromosome is attached to another non-homologous chromosome. (E) Crossing-over—in which the genes of two chromosomes interchange.

III. Gene Mutations. (A) Dominant mutation—all offspring carrying the mutant gene possess the new phenotype. (B) Recessive mutation—no phenotypic effect is noted (carrier state) unless the offspring receives the recessive mutant gene from both parents, or unless in the male offspring the recessive mutant gene is on that portion of the X chromosome that is unmatched by genes on the Y chromosomes. The classic examples of X chromosome sex-linkage are color blindness and hemophilia.

The first chromosome identified as a carrier of specific genes in man was the X chromosome [*16,40*]. It carries sex-linked genes, of which many have been identified. We postulate that the development of ovaries in normal females requires the presence of female-determining (sex) genes of two X chromosomes, since the presence of only one X chromosome has been demonstrated to produce vestigial gonadal streaks in the XO individual.

The second, and at present the only other identifiable chromosome for which specific genes have been claimed, is the Y chromosome [*16,29,40*]. Complete Y linkage indicates that a gene responsible for a certain trait is confined to the Y chromosome solely. The Y chromosome has been shown to be concerned with sex de-

termination in certain lower forms [*16*] and most recently has been demonstrated to be the bearer of male fertility in Drosophila busckii [*41*] and of male-determining factors of the mouse [*42*]. We postulate that the one trait which fits the definition of complete Y linkage in normal human subjects is the formation and development of testes, in contrast to the previously held theory of autosomal control of male-determination [*43*]. The formation of testicular elements would be dependent upon the presence of male-determining (sex) genes of a Y chromosome. With this concept, we postulate that the presence of the XX and XY combinations does not guarantee normal gonadal development unless the "sex" genes are normal and are in genetic balance with each other and with the autosomal genes. If an abnormal genetic balance is present because of non-disjunction, deletion, duplication, inversion, translocation, crossover or gene mutation, then gonadal sex may be abnormal. Autosomal genes may, in addition, influence the formation of abnormal gonadal development even in the presence of normal sex genes. The possibility of an abnormal hormonal environment or other environmental factors affecting the primordial gonads to produce abnormal gonadal differentiation must be considered, but these possibilities are probably less likely in the light of the following genetic evidence.

TURNER'S SYNDROME (GONADAL DYSGENESIS)

The eponym of Turner's syndrome [*44*] (Bonnevie-Ullrich-Turner syndrome) [*45*] refers to the association of certain congenital anomalies with gonadal aplasia (absence of all germ cells with lack of development of both the cortical and medullary components so that a vestigial streak composed of wavy connective tissue is seen in the broad ligaments) [*46*]. The name gonadal dysgenesis [*47*] has been proposed to include a large spectrum of embryonic defects in gonadal development.

Approximately 80 per cent of patients with classic Turner's syndrome have a chromatin-negative pattern in conjunction with a female appearance (phenotype) [*47–50*]. The reports of gonadal dysgenesis in "sisters" [*5,51–54*] and twins [*5,55*], combined with recent descriptions of abnormal chromosomal counts in certain persons with Turner's syndrome (45 chromosomes-XO) [*12,15a,15b,33–35,49,56*], suggest a genetic origin, with non-disjunction of the sex chromosomes in the XO patient as the probable etiology. The clinical condition of infantile female external genitalia, vagina, uterus and tubes is adequately explained by the experiments of Jost [*22*] in accordance with the principle that masculinization requires the presence of a fetal testicular hormone. Primary amenorrhea, lack of secondary sex development (breasts), and elevated urinary gonadotropins are probably secondary to the absence of estrogen in these phenotypic females.

Color vision studies in families of patients with Turner's syndrome suggest that non-disjunction may occur during spermatogenesis and the pattern may be /X/O [*15a,15b,56a,56b,57*]. A color-blind patient with gonadal dysgenesis and a chromosome complex of 45 has been described whose parents had a normal number of chromosomes. The father had normal color vision, but the mother showed a minor defect in color testing which suggested that she was a heterozygote [*56b*]. These data support the view that the spermatozoan lacked a sex chromosome and the ovum contained the X chromosome which carried the color-blind gene. However, the recent observation [*21b*] of a chromatin-positive patient with Turner's syndrome and a chromosome complement of 45 suggests that a paternally derived X chromosome (heterochromatic) produced the chromatin mass. In this case non-disjunction probably occurred during oogenesis and the X chromosome was supplied by the sperm (/O/X). It is likely that Turner's syndrome with a 45 chromosome complement can be caused by non-disjunction during spermatogenesis or oogenesis, the former process producing the greater incidence of viable cases (chromatin-negative).

Five patients with gonadal dysgenesis have been described with skin chromatin sections [*20e*] or chromosomal counts [*49*] indicative of an XO-XX mosaic. Ford [*49*] has suggested that such persons develop from XO zygotes. An XX cell, arising by non-disjunction in the XO embryo, would multiply because of the normal genetic constitution whereas an OO cell would be non-viable. Another possible mechanism for an individual to develop as an XO-XX mosaic is by simple loss of an X chromosome during mitosis of an XX zygote. Court Brown et al. [*32*] described a patient with an XO-XXX mosaic. Non-disjunction in an XX zygote at the first mitotic division could produce this combination [*49*].

The finding of three characteristic features (gonadal dysgenesis, dwarfism and congenital

somatic abnormalities) in individuals with 45 chromosomes (XO) suggests to us that the lacking sex chromosome (X or Y) contains genes which are necessary for normal development in these categories. (Fig. 1–1.) Two chromatin-negative patients with Turner's syndrome have been described who claimed to have menstruated [*56a,58*]; in one of them an XO chromosome complement was demonstrated [*56a*]. It is of interest that fertile female mice with an XO complement [*31*], and ten chromatin-negative human females with normal ovarian tissue have been described [*24,59–61*]. Although no chromosomal analyses have been performed on these ten females, it is possible that under certain genetic conditions an XO female might be fertile. Three instances of a presumptive translocation of part of a missing chromosome to another chromosome, which possessed an abnormal configuration, have been described [*62a,62b,62c*]. We suggest that a similar translocation of female-determining genes from a broken X chromosome to an autosome could, in the presence of a normal X chromosome, influence the formation of ovaries.

In the XO individual we suggest that the wide spectrum of somatic defects [*33,46,47,63,64*] is in part due to the presence of recessive genes in the X chromosome, or the resultant genetic imbalance of an XO combination. Haddad and Wilkins [*46*] studied fifty-five patients believed to have the complete form of gonadal aplasia. All were short in stature. When they were classified as to whether or not anomalies of the neck were present, it was found that coarctation of the aorta and lymphedema occurred only in patients with abnormal necks. On the other hand, abnormal facies, shield-like chest, cubitus valgus and idiopathic hypertension occurred with approximately equal frequency in the two groups. This study, and others which will undoubtedly follow, may help to clarify the etiology of sex-linked congenital anomalies. A patient with an XO chromosome complement has been described [*56a*] with gonadal aplasia, dwarfism and few somatic anomalies. In this subject we postulate that there were few abnormal recessive genes on the X chromosome, or that the autosomal balance was minimally disturbed.

Chromatin-positive patients with gonadal dysgenesis who have a 46 chromosome complement (XX as reported in one patient [*12*]) have fewer congenital somatic abnormalities than chromatin-negative (XO) persons [*46,47*]. The genes for gonadal differentiation and stature are probably closely associated on the sex chromosome (Fig. 1–1), since reports of individuals with gonadal dysgenesis but without dwarfism are rarely recorded [*23,64–67*]. In order for the typical syndrome to develop in a chromatin-positive individual with 46 chromosomes, a large aberration of the X chromosome (e.g., deletion)* would be necessary to include the genes affecting sex, stature and somatic characters. (Fig. 1–2.) A smaller deletion of the X chromosome, involving only the sex and stature genes, would account for the more common situation of gonadal aplasia with dwarfism seen in the chromatin-positive individual. (Fig. 1–3.) Incomplete forms of gonadal dysgenesis with nests of primordial follicles or hypoplastic ovaries have also been described [*53,58b,58c,66,68*]. A smaller deletion of the X chromosome involving a portion of the sex-determining genes is postulated in these chromatin-positive patients. (Fig. 1–4.) If the habitus of Turner's syndrome is also present, the deletion may have included the stature and appropriate somatic genes as well. Patients described with hypoplastic ovaries, "precocious menopause" and "sterile ovaries" may suffer from incomplete and unrecognized forms of gonadal dysgenesis, due to minimal deletion of female-determining genes on one X chromosome. (Fig. 1–4.)

A mild example of gonadal dysgenesis with no stature or congenital somatic abnormalities has been described in a female with 47 chromosomes (XXX), who had a "precocious menopause" [*25*]. The abnormal ratio between the sex chromosomes and autosomes in this XXX combination probably accounts for the defective gonadal development. "Superfemale," derived from the genetic nomenclature of Drosophila studies in which XXX females were first described [*43*], is not the best clinical description for this particular individual since underdeveloped breasts, infantile external genitalia, defective ovarian structure and inadequate hormonal output were present. Another XXX female, who is still menstruating, is being reported on by the same group [*32*] and until a definitive clinical syndrome is

* During the preparation of this paper, Stewart [*56*] suggested deletion as a possible factor in gonadal dysgenesis. Court Brown [*32*], upon reading our preliminary communication [*1*], informed us that his group is publishing a report of a woman with primary amenorrhea, infantile genitalia and primitive streaklike gonads who, they believe, has a partial deletion of one chromosome.

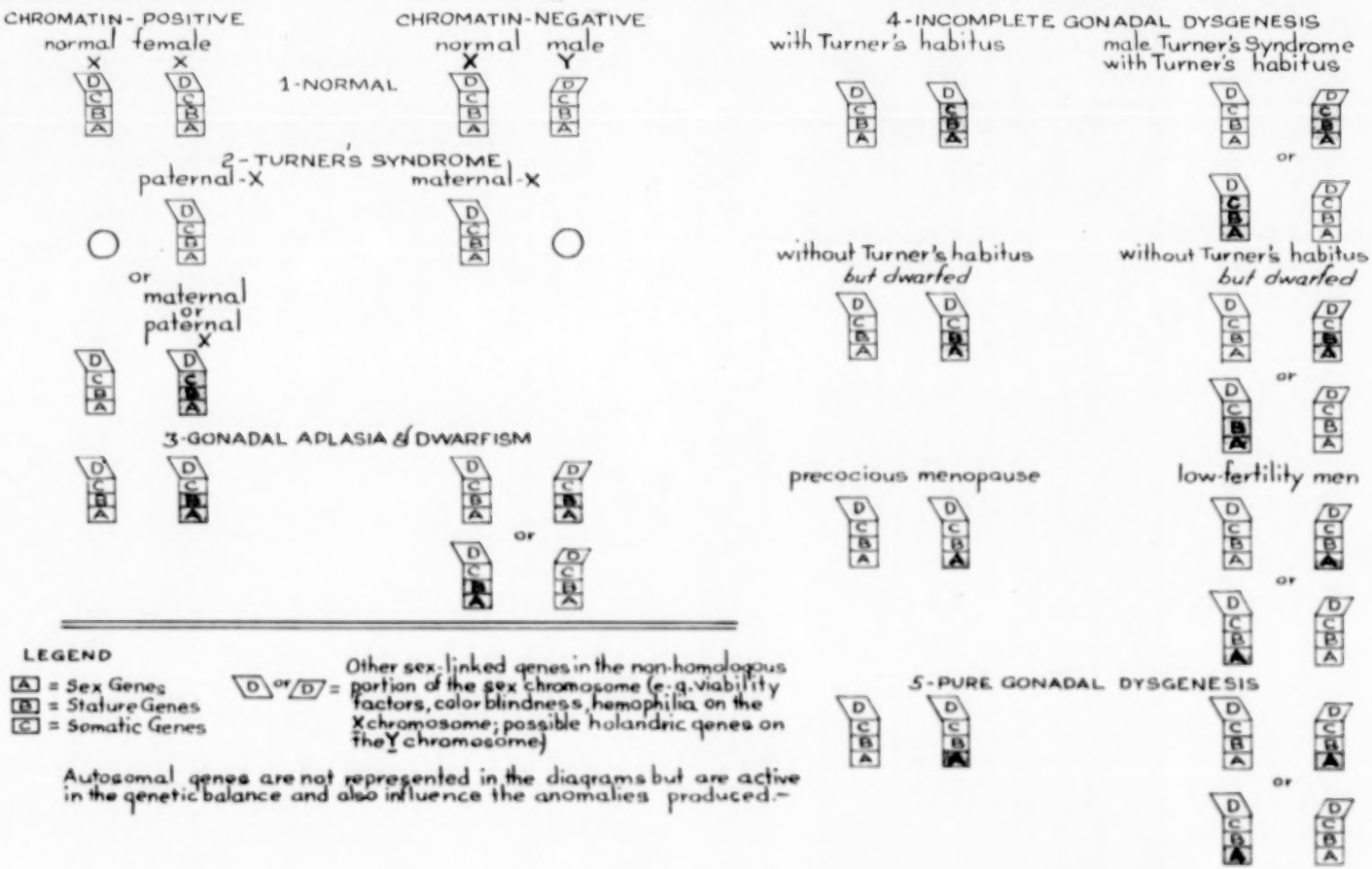

FIG. 1. Schematic representation of postulated defects of the X and Y chromosomes in gonodal dysgenesis.

finally established the genetic name would seem to be adequate.

Tall, thin, eunuchoid females have been described with chromatin-positive patterns (presumably XX) and vestigial streaks revealed by exploratory laparotomy (pure gonadal dysgenesis) [*58c,66,69*]. (Fig. 1–5.) We postulate that a deletion of the sex genes of one X chromosome resulted in faulty ovarian development. Similar clinical features have been noted in chromatin-negative patients [*70,71*]. One of these phenotypic females has been found to have an XY chromosome complement [*70*]. No laparotomy was performed to examine the gonads but all features suggested a "pure gonadal dysgenesis" (high gonadotropins, primary amenorrhea). The authors [*70*] state that they could not exclude a structural change in the chromosomes, too small to be detected by present technics. We postulate that a chromosomal deletion was the cause, involving either the sex genes of the Y chromosome or the sex genes of the X chromosome (Fig. 1–5). An autosomal gene mutation which may modify the action of the sex genes is another possible mechanism. However, no somatic anomalies were demonstrated in these patients, so that an autosomal influence cannot be established and deletion of sex genes may be a more likely cause.

Turner's syndrome in boys and men may be defined as the presence of some stigmata of Turner's somatic anomalies in conjunction with hypoplastic or undescended testes [*47,64,72*] (incomplete gonadal dysgenesis in our classification). (Fig. 1–4.) The presumed chromosomal constitution is XY (chromatin-negative). The report of two sibships [*72*] suggests a genetic etiology. The first sibship involved a "sister" with gonadal aplasia and a brother with some stigmata of the habitus of Turner's syndrome and no palpable right testicle (presumed abdominal cryptorchidism). The second sibship involved two brothers with multiple congenital anomalies of the Turner's syndrome and unilateral inguinal cryptorchidism. According to the previous postulations, the syndrome suggests a chromosomal aberration of the X or Y chromosome affecting the somatic, stature and sex genes, but enough of the sex genes remain in some persons to influence testes formation and male differentiation. An autosomal mutation affecting these three constituents of a sex chromosome appears to us to be a less likely possibility.

If the chromosomal aberration impaired the sex gene balance sufficiently to prevent the testicular elements from producing an adequate output of fetal testicular hormone, ambiguous external genitalia (male pseudohermaphrodite appearance) may be found in conjunction with the habitus of Turner's syndrome. A chromatin-negative infant has recently been described with this clinical picture [*73*].

Phenotypic females with a chromatin-negative pattern, the habitus of Turner's syndrome and vestigial medullary structures in the gonadal streaks [*47,58c,74*] may represent a severe form of this chromosomal aberration, manifested by no fetal testicular hormone output. Phallic enlargement and virilization after puberty may occur if the adult form of testicular hormone is produced by the vestigial medullary elements.

If the chromosomal aberration were to involve only a portion of the sex genes of either sex chromosome, leaving the stature and somatic genes intact, one might expect the production of dysgenetic testes with absent or low fertility in otherwise normal males. This is another form of incomplete gonadal dysgenesis in our classification (Fig. 1–4), to be discussed subsequently under seminiferous tubule dysgenesis [*75*].

KLINEFELTER'S SYNDROME (SEMINIFEROUS TUBULE DYSGENESIS)

Klinefelter's syndrome [*76*] refers to a group of phenotypically male individuals with a congenital disorder characterized by a specific abnormality of the seminiferous tubules. A broadened concept of the variable histological findings in individuals with congenital testicular defects has necessitated the introduction of a more general term to include multiple types of disorders of the seminiferous tubules (seminiferous tubule dysgenesis—S.T.D.) [*75*].

The majority of patients with Klinefelter's syndrome were found to have a chromatin-positive pattern associated with a male appearance [*48,50,75*]. The occurrence of this syndrome in families [*75,77,78*], and in identical twins [*79*] suggested a genetic origin of this type of testicular dysgenesis. Recent demonstration of a 47 chromosome count, including three sex chromosomes (XXY) in the chromatin-positive patients [*12,36–39,40*], substantiates the genetic origin and explains the chromatin-positive pattern on the basis of the presence of two X chromosomes. The presence of the Y chromosome in these patients causes the formation of testes (although dysgenetic) which secrete enough fetal testicular hormone to produce a male phenotype.

The origin of the XXY chromosome combination is believed to be non-disjunction of the sex chromosomes in the developing sperm or ovum [*15a,15b*]. Studies of color blindness tend to indicate that maternal non-disjunction (/XX/) is likely in these patients [*15a,15b,57,80*]. Two instances of a color-blind, chromatin-positive son exhibiting the Klinefelter syndrome, with parents who were not color blind, have been interpreted as showing evidence of non-disjunction in the maturation of the ovum [*80*], with doubling of the X chromosome carrying the color-blindness gene. However, a study [*20k*] revealing a statistically increased incidence of childless paternal uncles in chromatin-positive patients' families suggests that the uncles may have had a similar gonadal defect and in certain cases paternal non-disjunction may be present. It is probable that maternal or paternal non-disjunction may be responsible, just as in the individual who has 45 chromosomes and Turner's syndrome [*49,57*].

Since sperm are easily accessible, perhaps an electrophoretic technic of separation of the paternal sperm could reveal fathers with a tendency to produce XY and O sperm, which might then be differentiated from normal X or Y sperm on the basis of deoxyribonucleic acid content (method of Leuchtenberger [*20d*]).

A mosaic pattern containing two groups of cells has been found in one individual with Klinefelter's syndrome (XX-XXY) [*37*]. Loss of a daughter Y chromosome during mitosis of an XXY zygote could yield a mosaic of this type. The other 12 chromatin-positive patients with Klinefelter's syndrome whose chromosome counts are reported in the literature have not demonstrated a mosaic pattern [*49*].

The abnormalities of the chromatin-positive patient with Klinefelter's syndrome include small testes (primary micro-orchidism) [*81*], azoospermia and elevated levels of urinary gonadotropins with variable features of gynecomastia, mental deficiency and eunuchoidism [*76,82*]. The eunuchoid features are most prominent in the sole to pubis measurements; the arm span is not increased [*82*]. Recent data on incidence indicate that this syndrome is more common than originally believed. In a large series of newborns, Moore [*83*] found a chromatin-positive pattern in five of 1,911 unselected anatomically male infants, correlating well with another estimate of 0.1 to 0.2 per cent of all phenotypic males [*82*]. In a survey of mentally retarded males, 1.2 per cent were found to have chromatin-positive patterns [*81*]. In fertility clinics, approximately 20 per cent of the males with azoospermia were chromatin-positive [*20h*] or had female leukocyte patterns [*84*].

It is reasonable to assume that the development of dysgenetic testes is due to the abnormal ratio of female- to male-determining genes on the Y chromosome in the XXY combination. Chromatin-negative patients with Klinefelter's syndrome have fewer clinical characteristics of the syndrome than chromatin-positive individuals [*82*] and have a chromosomal complement of 46 (XY) [*12,37*]. The histologic difference [*20i,20j, 86a,86b*] between the testes of chromatin-positive and chromatin-negative patients is evidence of the different etiology. The testes in a chromatin-positive case is characterized by an irregular arrangement of partially and completely hyalinized tubules (tubular sclerosis) lying next to tubules of varying size which are lined by Sertoli cells. Germ cells may be found in a few single tubules although azoospermia is present. In addition the Leydig cells are prominent and frequently aggregated in groupings, possibly more pronounced because of surrounding tubular atrophy. In chromatin-negative patients a variable degree of abnormality is found, introducing the need for the term, seminiferous tubule dysgenesis (S.T.D.), to include other congenital defects of the seminiferous tubules. Some of these individuals have tubular sclerosis, but to a less severe degree than the chromatin-positive patient [*20i,20j,75*]. Other chromatin-negative subjects demonstrate germinal aplasia with tubules lined only by Sertoli cells [*85*] or a combination of tubular sclerosis and germinal aplasia [*86a*]. We would include in S.T.D. other forms of seminiferous tubule defects found in cryptorchidism [*86b*], Turner's syndrome in males [*86a*], male pseudohermaphrodites [*vide infra*] and low fertility males [*86b*] when these are on a genetic basis and not due to environmental factors.

A more general term for these defects in phenotypic males (XY) is "incomplete gonadal dysgenesis." (Fig. 1–4.) This designation could include those individuals with dysgenesis of all testicular elements, such as congenital anorchia [*86a,86c*]. If the male-determining genes on the Y chromosome had sufficient effect to influence the development of fetal testes, but insufficient effect to maintain them, testicular atrophy could occur. If the testes atrophied after formation of the fetal testicular hormone, one would see the

example of congenital anorchia associated with masculine internal and external genitalia [*60*]. If the defective testes atrophied before complete action of the fetal testicular hormone was accomplished, one would see congenital anorchia with mixed external genitalia (congenital anorchia with male pseudohermaphroditism) [*5*].

A genetic origin for variable testicular defects is supported by the observation [*87*] of a stock of otherwise normal healthy guinea pigs with an inherited male sterility. The pathologic condition of the testes varied from germinal aplasia to a slightly subnormal state. The etiology was believed to be due to a "male-limited factor of variable expressivity."

One might expect the variability of testicular disease found in chromatin-negative males with "incomplete gonadal dysgenesis" since a testicular defect may be induced by differing chromosomal aberrations or mutations involving the sex genes on the Y or X chromosome. In addition, certain autosomal genes may influence the genetic balance which is necessary for normal gonadal development. The association of gonadal defects with other congenital abnormalities affecting the vertebrae, thyroid and pancreas [*86a*] and the metacarpals [*88*], as well as the association of hypogonadism in congenital disorders of familial muscular dystrophy [*63*], myotonia dystrophica [*75,89*], some cases of the Laurence-Moon-Biedl syndrome [*77,86a*] and congenital anomalies with familial eunuchoidism [*77*], suggest that various abnormal autosomal genes may induce gonadal as well as somatic abnormalities in some patients.

The quoted higher incidence (60 to 75 per cent) of patients with the Klinefelter syndrome and chromatin-positive pattern than chromatin-negative pattern [*5,48,75*] may be because nondisjunction is more frequent than altered action of the male-determining genes on the Y chromosome. It is more likely, however, that the clinical and gonadal abnormalities in S.T.D. may be more prominent in chromatin-positive cases, and the chromatin-negative cases may include minor degrees of gonadal defects that previously had not been added to the group.

MALE PSEUDOHERMAPHRODITES

The term "male pseudohermaphrodite" refers to an individual with testes and ambiguous or female internal duct structures and/or external genitalia [*5*]. These individuals characteristically have chromatin-negative patterns and a chromosomal count of 46, with an XY sex chromosome combination [*11,15a,15b,90–92*]. The testes contain defective seminiferous tubules. In our classification male pseudohermaphrodites are considered to be another form of S.T.D. In phenotypic males a spectrum of defects may be seen, ranging from simple hypospadias with scrotal, inguinal or abdominal testes to the presence of abdominal testes with persistence of Wolffian and Müllerian duct structures [*5,93*]. Phenotypic females have testes located intra-abdominally, or in inguinal or labial hernias. Some patients have normal female habitus and external genitalia with a blind vaginal pouch, poor breast development, primary amenorrhea and absent or scanty axillary and pubic hair (complete form of testicular feminization) [*94*]. Others have fallopian tubes, a rudimentary uterus and vagina with a hypospadic penis (incomplete form of testicular feminization) [*5,93,94*]. The incidence of all forms of male pseudohermaphroditism is approximately 1:10,000 births [*93*].

The existence of a male pseudohermaphrodite and a normal male as non-identical twins [*5*] is evidence against the etiologic theory [*50*] of a maternal antitestis factor of a hormonal or antibody nature since the factor would be expected to be active on both twins. The high familial incidence of the "feminizing testes syndrome" is shown by the number of "sisters" and "maternal aunts" with the same findings [*91,92,94*]. The sterility of the patients prevents direct hereditary descent, but the history of Case 2 of Morris [*94*] describes five cases in three generations of the same family following the maternal line, suggesting a sex-linked genetic disorder. Familial cases also have been described in which the complete and the incomplete forms of testicular feminization were present in affected relatives [*5*]. We suggest that there may be a mutation of the sex genes on the X chromosome which is capable of modifying the action of the Y chromosome sex genes, resulting in partial fetal testicular insufficiency to the extent of allowing female-type duct or genitalia development. In addition, in phenotypic females there may be an enzymatic defect in the synthesis of testicular hormones with the production of abnormal hormones which stimulate feminine secondary sex characteristics after puberty [*94*]. Modification of the action of certain autosomal genes which influence the end organ sensitivity (breasts, axillary and pubic hair) to androgenic

stimulation [*95*] may also be affected by the mutation on the X chromosome.

Puck et al. [*92*] have recently postulated that the defective gene in male pseudohermaphroditism is autosomal, on the basis of the observation in such patients of color blindness and hemophilia which was also present in siblings with normal gonads. Since the genes responsible for "testicular feminization" were not closely linked to different X-linked genes, autosomal location was considered highly probable. However, we believe that the loci for the sex genes are distant from the mutant genes involved in color blindness and hemophilia so that crossing-over of these sections on the X chromosome is possible. The finding of a delayed menarche in three female members of the family quoted by Puck et al. does not rule out the possibility that the female-determining genes on the maternal X chromosome were at fault, causing male pseudohermaphroditism in an XY individual and delayed menarche in an XX individual, due to a dominant mutation.

Several patients with Klinefelter's syndrome and associated external genitalia anomalies of hypospadias and inguinal cryptorchidism have been described [*5,20j,32,78*]. Reifenstein [*78*] described a family in which nine of ten males in two generations demonstrated a clinical picture of Klinefelter's syndrome in association with hypospadias. Inheritance was believed to have been transmitted through the maternal line. A significant excess of childless maternal uncles was noted in the families of chromatin-negative patients with Klinefelter's syndrome [*20k,96*], suggesting that these uncles may also suffer from a similar gonadal defect. A maternal sex-linked mutation, somewhat similar to the mutation causing male pseudohermaphroditism, could modify the action of the male-determining genes on the Y chromosome and produce these findings in familial instances of Klinefelter's syndrome. Other familial cases of S.T.D. (germinal aplasia with tubular fibrosis [*86a*], Turner's syndrome in males [*72*]) may have their origin in a similar mechanism.

One case of "male pseudohermaphroditism" with a sex chromosome constitution XO has been mentioned in the literature [*97a*]. A personal communication from Dr. Ferguson-Smith [*97b*] describes this infant as having ambiguous external genitalia with perineal hypospadias, a testis with reduced number of germ cells on one side and a gonadal streak composed of "ovarian stroma" on the other, and bilateral tubes with a uterus. "He is thus a combination of unilateral male pseudohermaphroditism and gonadal aplasia" [*97b*]. A chromatin-negative patient with a testicle on one side, an undifferentiated gonad on the other side and a male pseudohermaphrodite appearance has also been described [*97c*]. Such individuals might arise from an XY zygote by loss of a Y chromosome during mitosis to produce an XY-XO mosaic. Ferguson-Smith [*97b*] is now studying more cells of his patient to determine whether a mosaic of this type is present. If a Y chromosome cannot be demonstrated, we postulate that male-determining genes were translocated from a broken Y chromosome to an autosome and were carried on this abnormal location into the process of fertilization. Evidence for the presumptive translocation of genes between a short and a long chromosome has been cited [*62a,62b,62c*]. The abnormal location of the male-determining genes could lead to the formation of dysgenetic testes with partial fetal testicular insufficiency and a resultant male pseudohermaphrodite appearance. Although the vestigial gonad may have the histologic appearance of "ovarian stroma," we believe that these individuals are not true hermaphrodites since ovarian follicles are not present. We classify these patients in the group of gonadal dysgenesis.

A case of male pseudohermaphroditism has been described as possibly having been produced non-genetically by large doses of estrogen administered to the mother early in pregnancy [*98*]. However, until reports of other such patients are recorded this child may have been a male pseudohermaphrodite on a genetic basis.

Female pseudohermaphrodites are individuals with normal ovaries in association with ambiguous external genitalia. The sex chromatin pattern is always positive [*5,99*]. Autosomal mutations most commonly producing congenital adrenal hyperplasia [*99*] or non-genetic hormonal disturbances can induce the abnormalities of the external genitalia [*20g,99*]. Since no sex chromosome or gonadal abnormality is present in female pseudohermaphrodites, detailed consideration of this group is not within the scope of this discussion.

TRUE HERMAPHRODITES

The diagnosis of true hermaphroditism requires the histologic demonstration of both testicular and ovarian tissue, or ovarian tissue and the presence of sperm in the semen [*75*].

These patients are invariably characterized by some degree of ambisexual development of the genital tract [*75,100*], particularly hypospadias and cryptorchidism [*101,102*]. In the patients with true lateral hermaphroditism an ovary is found on one side while a testis is found on the other side [*100,103*]. Rarely a separate ovary and testis is found bilaterally [*104,105*], or unilaterally with no gonad on the other side [*106,107*]. The merging of the ovarian and testicular elements produces ovotestes, which may be bilateral or may be associated with an ovary, a testicle or a vestigial streak on the opposite side. If a testis is present, Wolffian duct structures develop on that side. If an ovotestis is present, predominantly Müllerian duct structures develop although some Wolffian duct remnants may persist. If an ovary or no gonad is present, only Müllerian duct structures develop on that side [*5,106*].

True hermaphrodites were believed to arise by the process of non-disjunction of the X chromosome after the initial cleavage of the XY zygote [*26,100*]. If so, a mosaic of cells containing XY or XXY chromosomes would be present in the same individual [*38,100*]. YO cells would not be present because they are believed to be inviable [*49*]. However, the sex chromatin pattern was found to be the same from contralateral sides of the body in nine cases studied, thus eliminating the possibility of an XY-XXY mosaic [*5,108–110*]. The argument for a mosaic of XX-XXY in chromatin-positive cases is weakened by chromosomal counts of 46 (XX), without evidence of mosaicism, in multiple tissues examined from two true lateral chromatin-positive hermaphrodites [*110,111*]. Although one patient with true lateral chromatin-positive hermaphroditism has been described with a squash preparation of the testis suggesting an XXY constitution [*100,108*], chromosomal counts were not performed, so the karyotype in this case is not definitely established. A chromatin-negative true hermaphrodite with an ovary and a testis has been described with 46 chromosomes and an XY complement [*112*]. No evidence of mosaicism was mentioned in this case.

We have suggested that the usual development of functioning ovaries is dependent upon the presence of a normal complement of the female-determining genes on 2 X chromosomes and the absence of male-determining genes of a Y chromosome. The presence of ovaries in an XO individual, we believe, is due to translocation of X sex genes to an autosome. The formation of testicular elements is dependent upon the presence of male-determining genes of a Y chromosome in the presence of an X chromosome. The Y sex genes can overcome the presence of 2 X chromosomes to influence the formation of testes, as in the chromatin-positive patient with Klinefelter syndrome. The male-determining role of the Y chromosome is substantiated in human subjects by chromosomal count studies in the presence of testes in normal males (/X/Y) [*11–14,17*], chromatin-positive Klinefelter's syndrome (/X/XY or /XX/Y [*12,36,37–39*], chromatin-negative Klinefelter's syndrome (/X/Y) [*12,37*] and in male pseudohermaphrodites (/X/Y) [*11,15a,15b,90–92*]. The absence of a Y chromosome leads to the absence of testes, as noted in normal females (/X/X) [*11–14,17*], /XX/X females [*25,32*], and chromatin-negative (/X/O) [*12,33–35*] or chromatin-positive patients with Turner's syndrome (/X/X or /O/X) [*12,21b*].

Since recent evidence [*41,42*] suggests that the Y chromosome carries the genes responsible for testicular development, one may invoke the mechanism of incomplete Y linkage with crossing over or translocation of sex genes to explain the true hermaphrodite gonadal defects. In the rare situation of incomplete Y linkage, homologous loci in the X and Y chromosome crossover from one sex chromosome to the other, as described in certain lower forms [*40,113*]. It has often been observed that the homologous regions of the X and Y chromosome in the primary spermatocyte are associated end-to-end during meiosis to form a nucleolus-like heterochromatic body in mammals such as the rat, mouse [*114*] and man [*20a,20c*]. We suggest that the genes which influence sex determination are located in the homologous sections of the sex chromosomes, which form the terminal association. (Fig. 2.) The terminal association may represent genetic crossover or be the site of a translocation [*20c*]. In man, were such phenomena to occur, disturbance in gonadal development could be predicted, depending upon the number of male-determining genes located on that Y chromosome portion which becomes attached to the X chromosome, or female-determining genes of an X chromosome portion attached to a Y chromosome. The greater the amount of male-determining Y genes present in the X or Y chromosome, the stronger would be the tendency towards testicular development. The occurrence of crossing over or of a translocation during spermato-

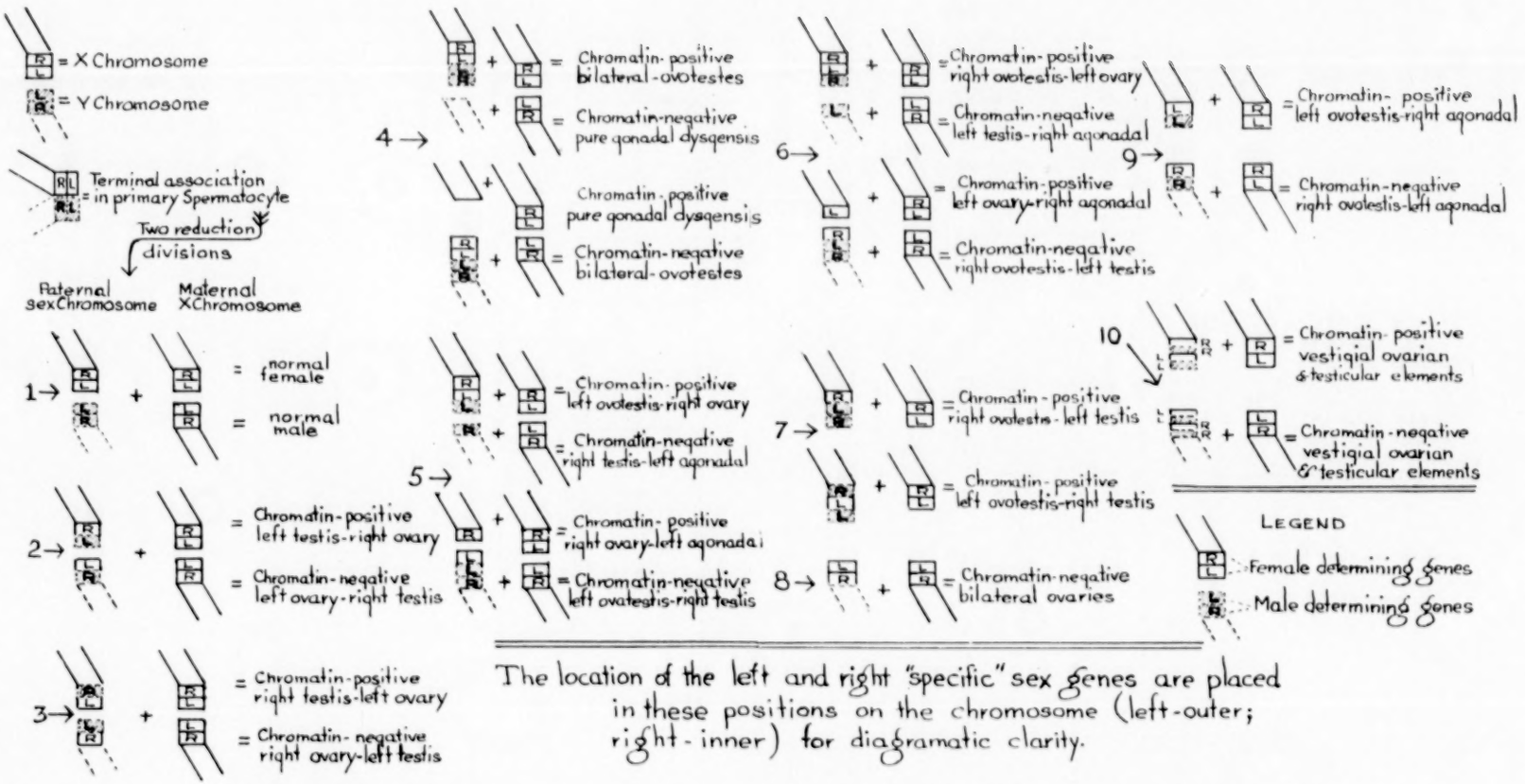

FIG. 2. Schematic representation of cross-over and translocation of sex genes as postulated for true hermaphrodites.

genesis may be signified by a connecting line above the sex chromosome combination, the first chromosome of the combination indicating the anatomical chromosome that is donated to the fertilized ovum ($\overline{XY}$ or $\overline{YX}$).

A genetic etiology for true hermaphroditism has been implicated in lower forms such as the pig and the goat [*5*]. Two sibships have recently been reported in man, one with chromatin-positive brothers [*102*], the other with chromatin-negative brothers [*105*], lending support to a genetic origin. We believe that the tendency for crossing over or translocation to occur during spermatogenesis was repeated for each brother. The infertility produced by the hermaphrodite status prevents direct transmission of this trait to further generations.

A review of the literature showed no definite relationship between either side of the body and the presence of an ovary or a testis on a specific side [*106,115,116*]. Animal experiments do not explain these findings [*117*]. In order to explain the appearance of an ovary and a testis on opposite sides, we suggest that there are closely associated but separate sex genes on the X and Y chromosome which control not only the differentiation of an ovary or testis but also on which side it develops. (Fig. 2–1.) We realize that the concept of a separate set of genes controlling a particular organ on each side of the body is a novel approach to this problem. Support for this concept may be found in the observation of a different color eye on each side, noted as a hereditary trait in certain animal families, including Angora cats [*118*] and the "wall-eyed" horse [*119*]. Gossage [*120*] described a human family in which nine of thirty-one individuals in five generations demonstrated this anomaly, always affecting the left eye (greyish blue with chestnut brown patches in the affected individuals). These observations suggest to us that autosomal genes may exert a separate influence on each side of the body in rare families. Certain patients with the clinical characteristics of Turner's syndrome exhibit a congenital asymmetry (hemihypertrophy) of the body [*121*]. In these individuals the genetic effects which influence shortness of stature were not as evident on one side of the body, allowing a unilateral more normal growth pattern and subsequent body asymmetry. Rea [*86c*] collected twenty-nine case reports of congenital unilateral anorchia and reported six cases of his own in which thorough exploration demonstrated only one testicle. We suggest that there was a deletion of the specific sex genes which influence the development of the testicle on the affected side (or mutation of an autosomal gene which may modify the action of the specific sex genes). The sterility of patients with these congenital gonadal defects prevents the transmission of unilateral gonadal defects to offspring, in contrast to the inheritance of a different eye color that can be observed in several generations.

With the concept of the unilateral action of specific sex genes we can explain all forms of true hermaphroditism by postulating crossing over or translocation of sex genes. The chromosome complement would be 46, but the chromatin-positive individual would have an $/X/\overline{XY}$ constitution and the chromatin-negative patient would have an $/X/\overline{YX}$ constitution. (Fig. 2.) Crossing over of all the Y chromosome sex genes which influence the left gonad to the X chromosome and the corresponding unilateral X chromosome sex genes to the Y chromosome would result in a chromatin-positive individual with a left testis and a right ovary, or a chromatin-negative individual with a left ovary and a right testis, depending upon whether the X or the Y chromosome were involved in fertilization. (Fig. 2–2.) A similar crossing over, involving only the sex genes which influence the right gonad, would result in a right testis and a left ovary in the chromatin-positive individual, or a right ovary and a left testis in the chromatin-negative individual. (Fig. 2–3.)

Translocation of the Y chromosome sex genes, which influence both gonads, to the X chromosome would result in bilateral ovotestes in the chromatin-positive individual. Translocation of the X chromosome sex genes, which influence both gonads, to the Y chromosome would result in bilateral ovotestes in the chromatin-negative individual. (Fig. 2–4.) Reciprocal deletion of the sex genes from one sex chromosome would result in an individual with "pure gonadal dysgenesis."

Translocation of the Y chromosome sex genes which influence only the left gonad to the X chromosome would result in a chromatin-positive individual with a left ovotestis and a right ovary. Translocation of the X chromosome sex genes which influence only the left gonad to the Y chromosome would result in a chromatin-negative individual with a left ovotestis and a right testicle. (Fig. 2–5.) Reciprocal deletion of the sex genes influencing the left gonad would

result in a left agonadal individual. A similar translocation involving only the sex genes which influence the right gonad would result in a right ovotestis and a left ovary in the chromatin-positive individual, or a right ovotestis and a left testicle in the chromatin-negative individual. (Fig. 2–6.) Reciprocal deletion of the sex genes influencing the right gonad would result in a right agonadal individual.

In the chromatin-positive individual with an ovotestis and a testis (Fig. 2–7) we postulate an alteration of the X chromosome by a translocation of the Y chromosome sex genes which influence one gonad (resulting in an ovotestis), and a crossing over of the Y chromosome sex genes which influence the other gonad (resulting in a testis). The chromatin-negative individual with an ovotestis and an ovary is the only type of true hermaphrodite that has not been described in the literature. We have reviewed all of the recorded cases of chromatin-tested true hermaphrodites [*75,102–106,108–110,122–127*], and have received a personal communication from Dr. Murray L. Barr [*128*] regarding unreported cases, without finding any individual in this category. Such individuals might occur if a translocation and a crossing-over of X chromosome genes were to alter the Y chromosome in the manner indicated.

Crossing-over of the X chromosome sex genes which influence both gonads may result in the chromatin-negative individual with bilateral ovaries if the Y chromosome sex genes were completely replaced by this process. (Fig. 2–8.) Ten chromatin-negative individuals have been reported with histological studies revealing normal ovarian tissue [*24,59,60,61*]. Since biopsies of the ovaries were performed without complete sectioning of the entire gonad, one cannot discard the possibility that some of these patients may have been examples of a chromatin-negative true hermaphrodite with bilateral ovotestes or an ovotestis and an ovary. The rare possibility of an XO individual with bilateral ovaries must also be considered. Chromosomal counts and the possible demonstration of testicular elements in future patients in this category may serve to resolve this problem.

Patients have been described [*106,107*] with ovarian and testicular elements on one side but a vestigial streak or no gonad on the other side. In these individuals we postulate the translocation of the sex genes which influence the side that had gonadal elements, and a deletion of the sex genes which influence the side that had no gonad. (Fig. 2–9.)

Since ovotestes can be considered an extreme differentiation of the dysgenetic gonad [*60*], we suggest that chromatin-positive [*60,66*] and chromatin-negative [*5,128*] individuals with vestigial ovarian and testicular elements may be true hermaphrodites, although they represent varying clinical pictures of gonadal dysgenesis. In the chromatin-positive patient, we believe that a portion of the Y chromosome sex genes crossover with a portion of the X chromosome sex genes. The resultant X chromosome, which is involved with fertilization, contains neither a full complement of X nor Y sex genes, and only vestigial gonadal structures develop. (Fig. 2–10.) A similar mechanism may apply to the chromatin-negative individual if the Y chromosome, containing an incomplete complement of Y and X chromosome sex genes, were to be involved in fertilization. This explanation could apply to those individuals who may be found to have a 46 chromosome complex.

The incidence of true hermaphroditism is low. Overzier [*115*] in 1955 collected only seventy-four valid cases after 1900, and Lewis [*101*] recently tabulated fifteen additional cases. Patients with these defects are now being reported with increasing frequency and there are other unpublished cases. The use of the skin biopsy and buccal smear technics undoubtedly will increase the rate at which cases are diagnosed by stimulating interest in the search for these patients among phenotypes who appear to be almost normal. Furthermore, if we apply the principles of crossing over or translocation, other cases may be included as true hermaphrodites although they represent varying clinical pictures of gonadal dysgenesis.

SUMMARY

1. A unified theory is presented to explain the origin of certain congenital gonadal defects on the basis of genetic imbalance involving the sex chromosomes (X,Y) and the autosomes. Nondisjunction of the sex chromosomes, chromosomal aberrations of the sex chromosomes (such as deletion, crossing over or translocation of sex genes between the X and Y chromosomes) and gene mutation have been implicated. (Chart 1.) The clinical characteristics of gonadal defects are reviewed and representative cases are included from the literature to support the theory.

Genetic Process Leading to Abnormal Sexual Development	Chromatin-Positive Individual	Chromatin-Negative Individual
Non-disjunction in the germ cell	/O/X (Gonadal dysgenesis) XXX ("Superfemale") XXY (Klinefelter syndrome)	/X/O (Gonadal dysgenesis)
Non-disjunction in the zygote	Mosaic individuals XX–XXY (Klinefelter syndrome)	XX–XO (Gonadal dysgenesis) XX–XO (Gonadal dysgenesis) XXX–XO (Gonadal dysgenesis)
Deletion or mutation of sex genes on the X or Y chromosome	XX individual Gonadal dysgenesis Ovarian hypoplasia "Precocious menopause"	XY individual 1. "Pure gonadal dysgenesis" 2. "Incomplete gonadal dysgenesis" a. Seminiferous tubule dysgenesis Klinefelter syndrome Germinal aplasia "Turner's syndrome in males" "Low fertility men" Male pseudohermaphrodite b. Congenital anorchia
Crossing-over or translocation involving the X and Y chromosome (bilateral or unilateral side-specific sex genes)	$X\overline{XY}$ 46 chromosome individual True hermaphrodite Some patients with gonadal dysgenesis who have "poorly differentiated ovotestes"	$X\overline{XY}$ 46 chromosome individual True hermaphrodite
Translocation of X sex genes to an autosome		XO (with bilateral ovaries)
Translocation of Y sex genes to an autosome		XO (male pseudohermaphrodite)
Autosomal mutation	XX individual Possibly present in those patients with various non-sex-linked congenital somatic defects associated with hypogonadism	XY individual

CHART 1. Postulated genetic defects in congenital gonadal disorders.

2. Non-disjunction of the sex chromosomes, during the development of the mature sperm or ovum, produces the more commonly recognized forms of gonadal dysgenesis (Turner's syndrome-XO) and seminiferous tubule dysgenesis (Klinefelter's syndrome-XXY) as well as the "superfemale" syndrome-XXX. Non-disjunction or loss of a sex chromosome in the zygote may give rise to mosaic patterns of XO-XX, XO-XXX, XX-XXY and XY-XO in a few individuals.

3. A chromosomal aberration (e.g., deletion of sex genes) is postulated as the basis for congenital defective ovarian development in chromatin-positive females with an XX sex chromosome complement.

4. Mutation or deletion of X or Y chromosome sex genes is postulated as the cause of certain congenital testicular defects in chromatin-negative individuals (XY) with Klinefelter's syndrome, germinal aplasia, Turner's syndrome in boys and men, low fertility, congenital anorchia or "pure gonadal dysgenesis." Male pseudohermaphroditism may be due to a hereditary mutation of the maternal X chromosome or a maternal autosome which is capable of modifying the action of the Y chromosome sex genes.

5. The linkage of sex determining genes located on the Y chromosome to an X chromosome by means of crossing over or by a translocation during spermatogenesis is postulated to be the cause of chromatin-positive true hermaphrodites. Similarly, the linkage of sex determining genes located on the X chromosome to a Y chromosome is postulated to cause chromatin-negative true hermaphrodites. A theory for the unilateral action of separate sex genes in the X and Y chromosome is presented to explain the different gonad on each side of the body in these

individuals. A broadened concept of true hermaphroditism to include some instances of gonadal dysgenesis with vestigial ovarian and testicular elements is suggested.

6. Translocation of female-determining genes from a broken X chromosome to an autosome may influence the production of ovaries in an XO individual. Translocation of male-determining genes from a broken Y chromosome to an autosome may influence the production of testes in an XO male pseudohermaphrodite.

7. Autosomal mutations may result in hypogonadism in certain individuals with non-sex-linked congenital somatic defects (evidence of the autosomal aberration).

8. Congenital anomalies associated with gonadal aplasia and dwarfism are known to occur in an XO individual. It is postulated that the varying somatic defects in Turner's syndrome may be related to the presence of recessive genes with deleterious effects on the X chromosome or the influence of genetic imbalance.

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ADDENDUM

Since this paper was submitted the following pertinent articles have been published.

A standard system of chromosome nomenclature has been established [*130*]. Court Brown and colleagues [*131*] reported a second female with an XXX sex chromosome complement, a female with deletion of a portion of one X chromosome, and a female with an XO-XXX sex chromosome mosaic. Two females who menstruated and had a possible XXX sex chromosome combination were described by de Carli et al. [*132*] and Sandberg et al. [*133*]. Fertile females with an XXX sex chromosome complex were recorded by Stewart and Sanderson [*134*] and Fraser et al. [*135*], the latter study suggesting an incidence of 0.7 per cent for this chromosome abnormality in mentally defective females.

An additional chromatin-positive patient with Klinefelter's syndrome and 47 chromosomes (XXY) has been reported by Leon et al. [*136*]. A second patient with the Klinefelter syndrome and an XX-XXY sex chromosome mosaic was recorded by Crooke and Hayward [*137*]. Ferguson-Smith et al. [*138*] reported on two patients with an XXXY sex chromosome constitution who demonstrated a greater degree of mental retardation and microorchidism than is usually seen in Klinefelter's syndrome, as well as the presence of double chromatin bodies in the intermitotic nuclei. Muldal and Ockey [*139*] described a chromatin-positive patient with Klinefelter's syndrome and a sex chromosome constitution of XXYY. The presence of the 2 Y chromosomes in this patient strongly supports the suggestion that non-disjunction may occur in the second maturation division in certain cases as predicted by Griboff and Lawrence [*140*].

Four true hermaphrodites with the sex chromosome complement of XX have been described by Ferguson-Smith et al. [*141*], de Assis et al. [*142*] and Gordon et al. [*143*]. One case of an XO–XY mosaic has been briefly reported by Hirschorn et al. [*144*]; histologic examination of one of the gonads revealed ovarian and testicular structures in an immature state.

A fertile female with an XO sex chromosome constitution has been reported by Bahner et al. [*145*] and two chromatin-negative females with ovaries have been described by Engstrom and Stoddard [*146*].

Penrose et al. [*147*] and Carter et al. [*148*] described chromosomal translocations involving the autosomes in familial mongolism.

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Studies on the Expanded Extracellular Fluid and the Responses to Various Stimuli in Primary Aldosteronism*

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INCREASES in the extracellular fluid (ECF) without alteration of plasma volume have been noted in subjects treated with adrenocorticotrophin and with cortisone [*1*]. In normal subjects given desoxycorticosterone acetate [*2,3*] and *dl*-aldosterone-21-monoacetate [*4*], a rise in both extracellular fluid and plasma volume has been reported. This expansion preceded any significant depletion of intracellular potassium, which might in itself have led to an increase in the extracellular fluid [*5,6*]. The prolonged and excessive endogenous secretion of aldosterone in primary aldosteronism would be expected to cause a comparable expansion. The availability of two patients with primary aldosteronism afforded an opportunity to measure changes in the extracellular fluid and alterations in aldosterone secretion when effective stimuli were applied before and after surgical removal of the tumor.

METHODS

During the experimental period the patients were maintained on a constant low sodium diet (10 and 16 mEq. sodium daily).† When a high salt intake was to be maintained, supplemental sodium was administered as weighed sodium chloride capsules. Fluid intake was kept constant. The patients were weighed daily. Urine was collected in twenty-four hour periods and stools in four day periods. Both were analyzed for sodium and potassium by internal standard flame photometry and for nitrogen by the Kjeldahl procedure. Serum sodium, potassium, chloride [*7*] and carbon dioxide content [*8*] were determined at appropriate intervals.

Aldosterone concentration of adrenal vein plasma (obtained at surgery) and urinary aldosterone were determined by the double isotope derivative assay technic of Kliman and Peterson [*9*]. The aldosterone content of the left adrenal gland and adrenal adenoma from one patient was analyzed as follows. Samples of tissue weighing 0.5 to 1 gm. were homogenized in 50 per cent ethanol, using a "Virtis 45" homogenizer, and centrifuged. The supernatant fluid was removed and diluted to a 20 per cent ethanol solution. An aliquot was treated with petroleum ether to remove lipids and then extracted with dichloromethane to obtain the aldosterone for assay.

Total blood, plasma and red cell volumes were measured using radioiodinated serum albumin [*10*], Cr^{51}-tagged red cells [*11*] and T-1824 [*12*].‡ During the expansion and contraction studies, Cr^{51} and T-1824 technics were performed daily in one patient, and Cr^{51} and radioiodinated serum albumin in the other. Predicted values of total blood volume, plasma volume and red cell volume were based on height and weight as described by Wennesland et al. [*13*]. Extracellular fluid was assessed by the inulin volume of dilution technic with normal values expressed as 16.2 per cent of body weight [*14*]. Na^{22} was used to estimate exchangeable sodium content [*15*].§

The glomerular filtration rate (GFR) was established by the clearance of inulin [*16*] in the fasting patients. Urine was collected by indwelling catheter (except in the preoperative study of R. T. (Case II) at intervals of twenty to thirty minutes, except during the diuresis accompanying the saline infusion when collections were made every ten to twenty minutes. The bladder was not washed when the urine flow exceeded 10 ml. per minute. Endogenous creatinine clearance was used to assess GFR during administra-

† Calculated and analyzed according to BOWES, A. DEP. and CHURCH, C. F. Food Values of Portions Commonly Used," 7th and 8th ed., 1951 and 1956. Philadelphia, College Offset Press.

‡ Performed by Dr. J. Hopper, Jr. and Dr. H. Yamauchi, Department of Medicine.

§ Performed by Dr. K. McCormack, Department of Radiology.

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tion of human growth hormone. Osmolality of serum was determined by the freezing point depression method.

CASE REPORTS

CASE I. L. B., a thirty-nine year old white woman, was referred to the University of California Medical Center from another hospital on March 10, 1959, with a diagnosis of primary aldosteronism. Hypertension, first recognized in 1941, had been noted again in 1944 following a streptococcal infection. Urinalysis showed trace amounts of protein but no renal casts; two-hour phenolsulfonphthalein excretion was 54 per cent. Subsequently, the patient complained of occasional pulling sensations in the legs and poor stamina.

In 1952, during her first pregnancy, the blood pressure ranged from 180/100 to 230/130 mm. Hg, but no protein was found in the urine. Labor was induced three weeks before term and a normal child was delivered. During the first three postpartum months the patient complained of being continually tired; episodes of extreme weakness but no loss of consciousness occurred on two occasions. Physical examination in 1952 showed a blood pressure of 220/130 mm. Hg and slight enlargement of the heart. Hematocrit was 31 per cent. Serum sodium concentration was 150 mEq. and serum potassium was 1.9 mEq. per L. An electrocardiogram showed changes typical of hypokalemia. Urinary specific gravity was 1.015. Phenolsulfonphthalein excretion was 72 per cent in two hours. Urinary 17-ketosteroid excretion and response to the administration of benzodioxane were normal. Perirenal air insufflation revealed no abnormalities.

A regimen of 3 to 6 gm. of potassium chloride daily with no restriction of dietary sodium resulted in mild symptomatic improvement; no further episodes of weakness occurred. During the next six years, serum potassium levels ranged from 1.9 to 3 mEq. per L., and blood pressure from 180/100 to 220/140 mm. Hg.

In 1955 the patient had an uneventful second pregnancy. On examination in 1958 persistent hypertension and hypernatremic, hypokalemic alkalosis were again noted while the patient's dietary intake of salt was normal. Nocturia, dryness of mouth, and weakness were continuing symptoms. Urinary aldosterone excretion* determined on two occasions was 53 and 75 μg. per twenty-four hours, respectively (normal 3 to 10 μg. per twenty-four hours).

At the time of hospitalization on March 10, 1959, the patient's blood pressure was 220/120 mm. Hg and pulse 72 per minute. Slight cardiomegaly and grade II hypertensive retinopathy were noted. Trousseau's sign was positive. She had hirsute legs, but a female escutcheon. No edema was noted.

The hemoglobin was 11.9 gm. per 100 ml., hematocrit 36 per cent. Specific gravity of the urine was 1.010 and pH was 6.8. Blood urea nitrogen was 15 mg. per 100 ml. Serum electrolytes, expressed in mEq. per L., were as follows: sodium 150, potassium 1.9 and chloride 95; carbon dioxide was 36 mM per L. An electrocardiogram showed changes characteristic of hypokalemia. An x-ray film of the chest showed slight cardiac enlargement and apical fibrocalcific changes. The GFR (inulin) was 95 ml. per minute. Phenolsulfonphthalein excretion was 60 per cent in thirty minutes. After fifteen hours of dehydration the serum osmolality had increased from 304 to 310 mOsm per L., and urine osmolality from 215 to 324 mOsm. per L. Subcutaneous administration of 15 units of Pitressin® increased urine osmolality to only 402 mOsm. per L. Repetition of these procedures immediately after potassium replacement (day sixteen) evoked essentially the same response. Retroperitoneal air studies showed borderline enlargement of the left adrenal gland. Urinary aldosterone levels determined on two occasions while the patient's daily sodium intake was 114 mEq. were 19 and 34 μg. per twenty-four hours (normal values in our laboratory 3 to 13 μg.). Urinary catecholamines were normal.

After completion of the clinical and investigative studies, a transabdominal exploratory operation was performed on June 17, 1959.† The right adrenal was normal in size. The left adrenal, weighing 7.6 gm., and an adenoma, weighing 8.4 gm., were removed. On microscopic examination of the adenoma it was seen that all three zones of the adrenal were represented. The zonal structure of the left adrenal was normal. A wedge biopsy of the kidney showed thickening of Bowman's capsule, some glomerular hyalinization and arteriosclerosis. Potassium retention occurred immediately after the operation, and within three weeks serum electrolyte levels had returned to normal. At this time the urinary aldosterone excretion had fallen to 3 μg. per twenty-four hours. Blood pressure six weeks after the operation was 148/90 mm. Hg. Nocturia and dryness of the mouth had disappeared. Trousseau's sign was negative.

CASE II. R. T., a twenty-five year old white man, was admitted to H. C. Moffitt Hospital on May 30, 1959, for evaluation of severe hypertension first diagnosed at age eighteen. At age twenty he had a questionable genitourinary tract infection and cylindruria. Blood pressure at that time was 190/130 mm. Hg. The hypertension responded poorly to treatment with reserpine, mecamylamine and chlorothiazide, which he continued to take up to the time of the present admission. Chlorothiazide alone without potassium supplementation had produced an episode of generalized weakness. He had persistent headaches, mild polyuria and nocturia.

At the time of admission, the patient's blood pressure was 220/130 mm. Hg. He appeared normal and

* Performed in the laboratory of Dr. F. C. Bartter, National Institutes of Health, Bethesda, Maryland.

† Expert supervision by Dr. Maurice Galante, Department of Surgery, is gratefully acknowledged.

in no distress. Physical examination showed cardiomegaly, a grade II apical mid-systolic murmur, and grade II hypertensive retinopathy. Trousseau's sign was positive. No edema was noted.

The hematocrit was 38 per cent. The serum sodium concentration was 150 mEq. and potassium 1.9 mEq. per L. Serum creatinine was 1.0 mg. per 100 ml. and endogenous twenty-four hour creatinine clearance 99 ml. per minute. The specific gravity of the urine was consistently below 1.014; the pH ranged from 6 to 6.5. Urine cultures were negative. An x-ray film of the chest showed moderate enlargement of the heart. Intravenous pyelograms were within normal limits; no evidence of an adrenal tumor was seen by retroperitoneal pneumography. Urinary catecholamine excretion was normal. Overnight dehydration followed by 15 units of Pitressin given subcutaneously showed minimal increases in urinary osmolality.

Chlorothiazide and subsequently potassium supplementation were discontinued after admission. Three weeks later, serum electrolyte concentrations, in mEq. per L., were as follows: sodium 153, potassium 1.9, chloride 92, carbon dioxide content 43 mM per L. Hematocrit was 37 per cent. Urinary aldosterone excretion was 35 μg. per twenty-four hours (normal 3 to 13 μg. per day). The patient's daily dietary sodium intake was 250 mEq. at this time.

After completion of clinical investigation a transabdominal exploratory operation was performed on August 17, 1959. The right adrenal was normal in size. The entire left adrenal, weighing 7.5 gm., and an adenoma weighing 4.5 gm. were removed. Microscopically, the tumor tissue was composed of large lipid-containing cells similar to those of the zona fasciculata. The excised adrenal had normal zonation; the zona glomerulosa was slightly hyperplastic. Needle biopsy of the kidneys showed normal renal structure. Two weeks after the operation the serum electrolyte concentrations, in mEq. per L., were as follows: sodium 140 and potassium 4.1; carbon dioxide content was 32 mM per L. Blood pressure was 200/110 mm. Hg, and the headaches had disappeared. Four weeks after the operation urinary aldosterone excretion was 5 μg. per twenty-four hours, and renal concentrating power had been restored. Seven months after operation the blood pressure was 160/100 mm. Hg.

RESULTS

Quantitation of Preoperative Extracellular Fluid Volume and Aldosterone Secretion. Measurement of extracellular fluids: The results of preoperative measurements, made while the patients were on constant metabolic balance, are summarized in Table I. The total blood volume was significantly increased in both cases. The rise was due exclusively to a change in plasma volume. Total exchangeable Na^{22} content was 52 mEq. and 63 mEq. per kg. body weight in Case I and Case II, respectively.

TABLE I
PREOPERATIVE MEASUREMENTS OF EXTRACELLULAR FLUID COMPARTMENTS IN L. B. (CASE I) AND R. T. (CASE II)

Compartment	Observed (L.)	Predicted (L.)	Deviation (%)
Case I			
Total blood volume	5.06	3.50	+45
Plasma volume	3.48	1.97	+76
Red cell volume	1.58	1.53	+ 3
Extracellular fluid (inulin)	13.0	8.3	+58
Case II			
Total blood volume	6.59	5.15	+28
Plasma volume	4.37	2.95	+48
Red cell volume	2.22	2.20	+ 1
Extracellular fluid (inulin)	19.0	12.2	+57

Urinary aldosterone: In Case I the mean of nine urine collections (twenty-four hours each) on a 114 mEq. sodium intake was 29 μg. (range 19 to 40 μg.). On day four (Fig. 1), one patient (L. B.) showed a diurnal variation in eight hour aldosterone excretion: from 8 A.M. to 4 P.M., 8 μg. per eight hours; from 4 P.M. to 12 midnight, 27 μg. per eight hours; from 12 midnight to 8 A.M., 5 μg. per eight hours. This pattern persisted, but at higher levels, during the period of potassium replacement (day sixteen). Twelve hour urinary aldosterone determinations on two other occasions, on a similar sodium intake, revealed a nocturnal excretion three times the daytime output (8 A.M. to 8 P.M., 8 μg. per twelve hours; 8 P.M. to 8 A.M., 30 μg. per twelve hours).

In the second patient (R. T.) the mean of six urine collections (twenty-four hours each) was 40 μg. (range 37 to 50). The normal range for urinary aldosterone in this laboratory on sodium intakes above 100 mEq. per twenty-four hours is 3 to 13 μg. per twenty-four hours.

Factors Known Normally to Alter the Extracellular Fluid. High sodium intake (Fig. 1): The salt intake of both patients was 114 mEq. sodium daily for two four day periods, separated by a twelve day interval of salt restriction.

In Case I (Fig. 1) urinary excretion of aldosterone during the periods of high salt intake

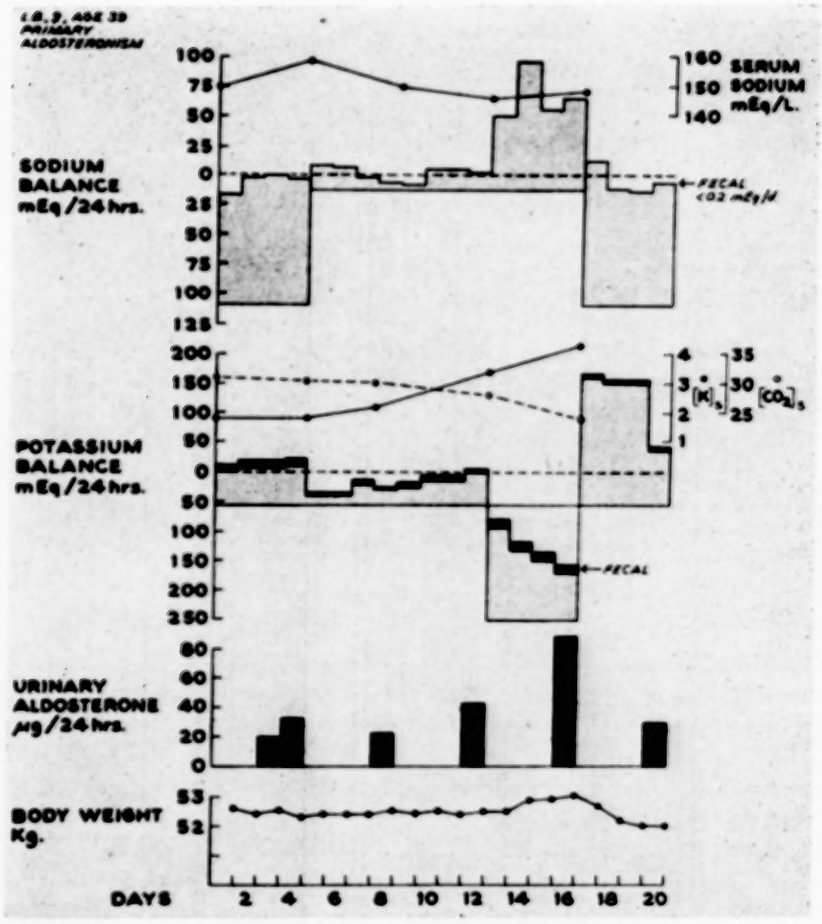

FIG. 1. Effect of high and low sodium intakes and potassium loading on sodium and potassium balance, serum electrolyte levels, urinary aldosterone excretion and body weight in L. B. (Case I).

(day one through four, seventeen through twenty) was essentially unchanged from the mean control value of 29 µg. per twenty-four hours. During the same periods serum potassium averaged 1.9 mEq. per L., and serum carbon dioxide content 33 mM per L. After resumption of a high sodium intake on day seventeen, sodium balance was rapidly achieved, without retention, and a fall in serum potassium to 3 mEq. per L. occurred in four days. Negative potassium balance and virtually no fecal sodium were noted.

In Case II resumption of a high sodium intake after a similar period of sodium restriction was followed by prompt adjustment within forty-eight hours, with no sodium retention or gain of weight. Urinary aldosterone excretion during the two periods of high sodium intake was 35 and 50 µg. per twenty-four hours, respectively, compared to a mean control value of 40 µg.

Sodium restriction: In L. B. (Fig. 1, day five through twelve), a salt intake of 10 mEq. daily for eight days resulted in immediate potassium retention. Adjustment to the lowered sodium intake was extremely rapid, without change in weight, hematocrit or hemoglobin concentration. Serum potassium rose from 1.9 to 3.3 mEq. per L.; serum carbon dioxide content fell from 33 to 28 mM per L. Urinary aldosterone excretion increased slightly from 29 to 40 µg. per twenty-four hours on the eighth day. The Trousseau sign was no longer obtainable by day twelve and the hypokalemic electrocardiographic changes disappeared.

In Case II a three day period of salt restriction (16 mEq.) also resulted in immediate potassium retention. Adjustment to this low sodium intake occurred within forty-eight hours. Serum potassium and carbon dixiode levels were unchanged.

High sodium intake and desoxycorticosterone acetate

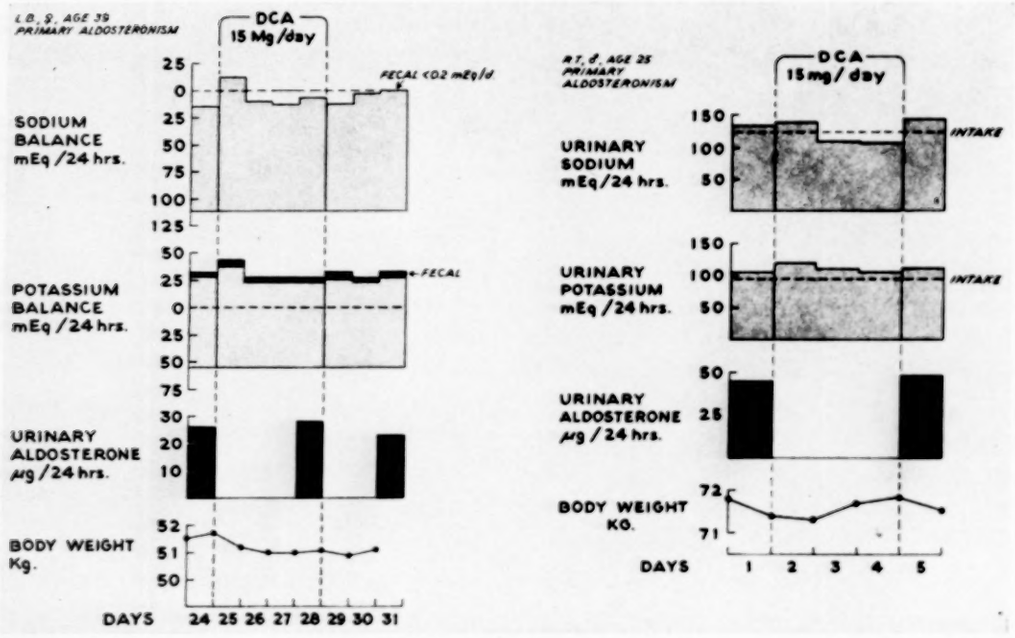

FIG. 2. Effect of the administration of desoxycorticosterone acetate on sodium and potassium balance, urinary aldosterone excretion and body weight in L. B. (Case I) and R. T. (Case II).

*(DCA) or dl-aldosterone-21-monoacetate:** During this study the dietary intake of sodium was 114 mEq. daily. As shown in Figure 2, daily intramuscular injections of 15 mg. of DCA to L. B. (Case I) for four and to R. T. (Case II) for three days failed to produce marked sodium retention or to alter urinary aldosterone excretion. Potassium wasting continued but was not increased. Similarly, intravenous administration of 1 mg. of *dl*-aldosterone-21-monoacetate to L. B. (Case I) over a four hour period had no effect on urinary excretion of sodium and potassium for six successive four hour periods.

Intravenous sodium loading: The results of rapid infusion of 0.9 per cent saline solution to L. B. (Case I), 50 ml. per minute, and R. T. (Case II), 33 ml. per minute, for sixty minutes are shown in Figure 3. In both patients, venous hematocrit dropped 9 per cent during the infusion, returning to control value within three hours. The urinary excretion of sodium was accelerated. During the infusion period, L. B. (Case I) excreted 38 per cent of the administered sodium load and R. T. (Case II) excreted 24 per cent. At the end of two and a half and three hours, respectively, L. B. (Case I) had excreted 78 per cent and R. T. (Case II) 45 per cent of the load.

† Both agents were kindly furnished by Dr. C. Sullivan of CIBA Pharmaceutical Products, Inc., Summit, New Jersey.

In both patients, maximum natriuresis occurred during the infusion period, averaging 4,450 µEq. per minute in Case I and 1,930 µEq. per minute in Case II. Maximum diuresis of 40 ml. per minute in Case I and 18.4 ml. per minute in Case II also occurred during the infusion. Glomerular filtration rate increased rapidly from 95 to 132 ml. per minute in Case I and from 120 to 158 ml. per minute in Case II; this rate was sustained throughout the infusion period of sixty minutes. During the control periods of the inulin clearance test, L. B. (Case I) excreted an amount of potassium equivalent to 24 per cent and R. T. (Case II) 30 per cent of that filtered, which was slightly increased during sodium loading. In Case I solute-free water clearance rose from 0.5 to 18.8 ml. per minute during the height of the diuresis. Venous pressure and pulse rate remained unchanged during the infusions. In this patient the blood pressure rose from 170/110 to 220/120 mm. Hg during the first fifteen minutes of the infusion but returned to base line levels when diuresis began In Case II blood pressure was not changed.

Plasma infusion: The results of intravenous infusion of 750 ml. of Plasmanate®† during a sixty-minute period in both patients are shown in Figure 4. On the day of infusion, dietary

† Radiated human plasma, Cutter Laboratories, Berkeley, California.

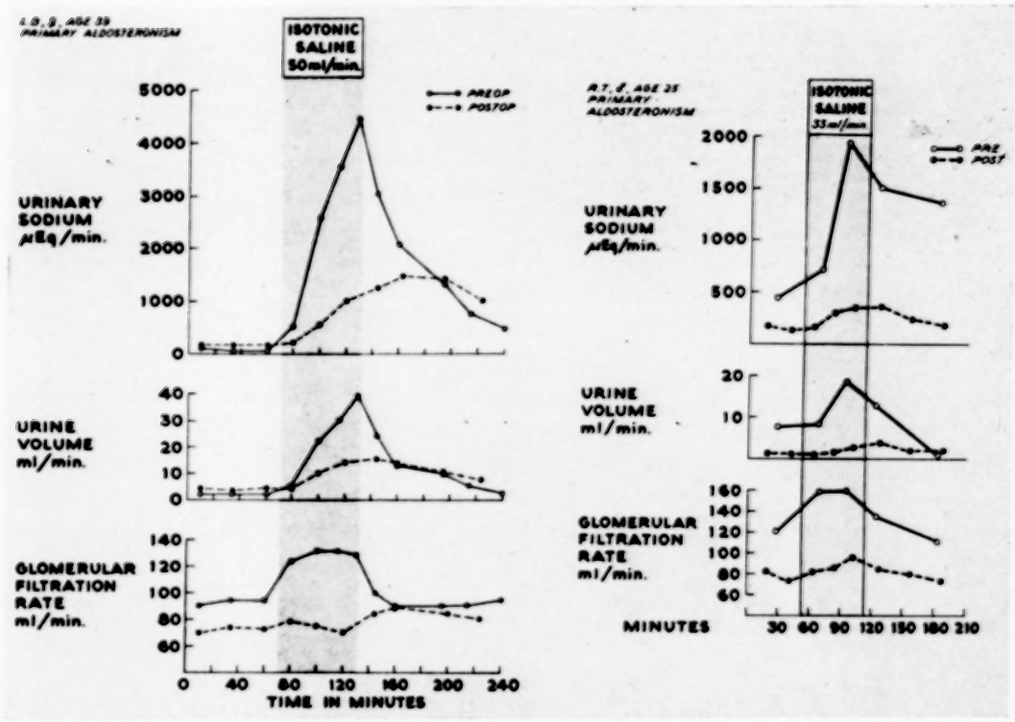

FIG. 3. Effect of 0.9 per cent saline infusions on the rate of urinary sodium excretion, urine flow and glomerular filtration rate in L. B. (Case I) and R. T. (Case II).

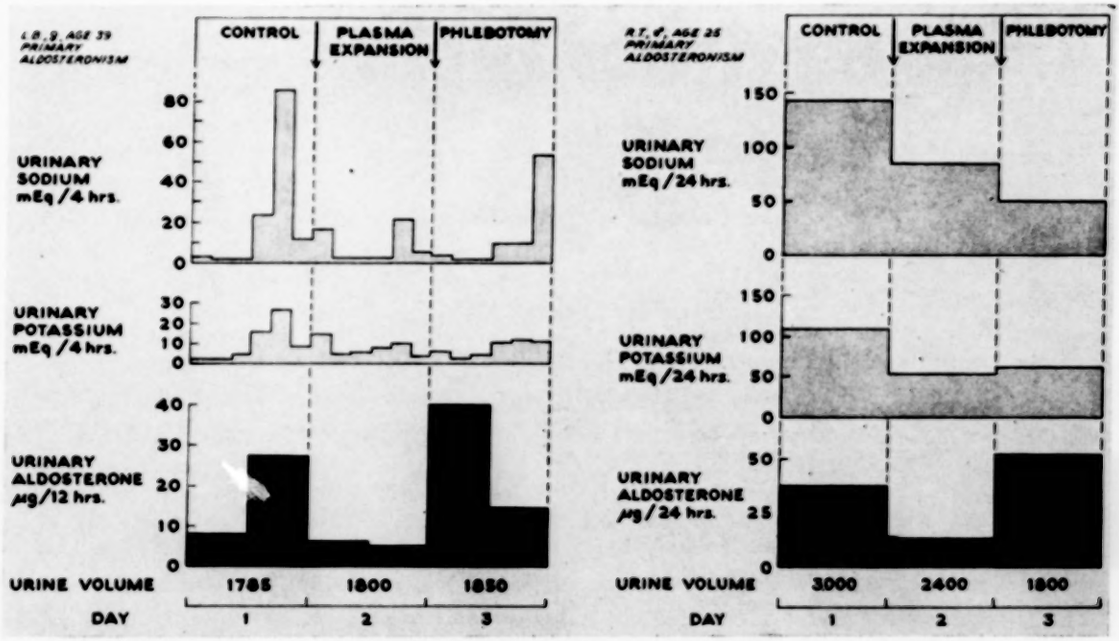

FIG. 4. Effects of infusion of 750 ml. of Plasmanate and subsequent removal of 400 ml. of blood on urinary sodium, potassium and aldosterone excretion in L. B. (Case I) and R. T. (Case II).

TABLE II
RESPONSES OF URINARY ALDOSTERONE TO VOLUME-INDEPENDENT AND VOLUME-DEPENDENT STIMULI IN CASE I AND CASE II

Study	Case I		Case II	
	Control (μg./24 hr.)	Experimental (μg./24 hr.)	Control (μg./24 hr.)	Experimental (μg./24 hr.)
Volume Independent Stimuli				
Stimulation				
ACTH	29*	110	40¶	85
Potassium loading	29	85	...	...
SU 4885	8/27†	6/70	50	5
Suppression				
Potassium depletion	85‡	29	...	...
Volume Dependent Stimuli				
Stimulation				
Salt deprivation	29	40§	...	...
Phlebotomy	8/30	40/13	37	54
Spirolactone	29	53	45	90
Suppression				
Blood volume expansion	8/30	6/5	37	11
Salt loading and DCA	28	29	40	48
Human growth hormone	8/30	6/9	50	18, 24**

* Mean of nine control days, range 19 to 40 μg./24 hours.
† μg./12 hours.
‡ Urinary aldosterone after potassium replacement.
§ Eighth day of salt restriction.
¶ Mean 40 μg., range 37–50 μg./24 hours.
** Experimental and following day.

sodium was reduced to compensate for the salt content of the Plasmanate. A transient sodium diuresis occurred in both patients during the first four hours after the infusion. During the first eight hours the urine output was 750 ml. greater than that of the control day in Case I and 490 ml. greater in Case II. In Case I a plasma volume expansion of 400 ml. was observed five hours after completion of the infusion. After twenty-four hours the total blood, plasma and red cell volumes were unchanged, but sodium retention amounted to 68 mEq. in Case I and 60 mEq. in Case II. Urinary aldosterone excretion decreased from a control value of 38 to 11 μg. per twenty-four hours in Case I and from a control value of 37 to 11 μg. per twenty-four hours in Case II. In Case I maximum suppression of aldosterone excretion occurred at night. Twelve hour endogenous creatinine tests showed little change during the control and infusion days. A weight gain of 0.2 kg. in Case I and 0.5 kg. in Case II was observed.

Phlebotomy: Removal of 400 ml. of blood from the patients the day after the plasma infusion resulted in an increase in urinary excretion of aldosterone. (Fig. 4.) In Case I, twenty-four-hour excretion was 53 μg., compared to a control value of 38 μg. Most of this rise occurred during the first twelve hours, whereas on the control day excretion was 8 μg. the first twelve hours. In Case II twenty-four hour excretion was 54 μg., compared to a control value of 37. Sodium retention was increased in both patients.

Factors Known Normally to Alter Aldosterone Secretion. Intravenous adrenocorticotrophin (ACTH) (Table II): In Case I 20 USP units of ACTH* given intravenously during a period of eight hours increased urinary 17-hydroxycorticoids from 10.4 to 40.4 mg. per twenty-four hours, urinary 17-ketosteroids from 13.7 to 17.7 mg. per twenty-four hours, and urinary aldosterone from 29 to 110 μg. per twenty-four hours. In Case II after the similar administration of 20 USP units of ACTH, urinary 17-hydroxycorticoids rose from 14 to 29 mg. and 17-ketosteroids from 20 to 37 mg. per twenty-four hours; urinary aldosterone excretion increased from 40 to 85 μg. per twenty-four hours.

Intravenous administration of SU-4885 (2-methyl-1-2 bis (3 pyridyl)-1-propanone)† (Table II): SU-4885, an inhibitor of adrenocortical 11-β hydroxylase [17], in doses of 30 mg. per kg. of body weight given intravenously for a period of four hours produced characteristic inhibition of cortisol synthesis and increased excretion of 11-desoxycortisol. In Case I urinary aldosterone excretion rose to 76 μg. per twenty-four hours (control value, 35 μg.). During the first twelve hours urinary aldosterone was not significantly decreased (6 μg. was excreted compared to a control value of 8 μg.); during the second twelve hours, urinary excretion rose to 70 μg. (control value 27 μg. per twelve hours). In Case II aldosterone secretion was inhibited, as evidenced by a fall in urinary aldosterone excretion from a control value of 50 μg. to 5 μg. per twenty-four hours.

Potassium loading (Fig. 1, days thirteen through sixteen): In Case I after eight days of low salt intake, serum potassium had increased from 1.9 to 3.3 mEq. per L., serum carbon dioxide

* "Corticotropin Injection," for which we are indebted to Dr. H. C. Peltier, The Upjohn Company, Kalamazoo, Mich.

† Methopyrapone supplied through the courtesy of Dr. C. Sullivan of Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

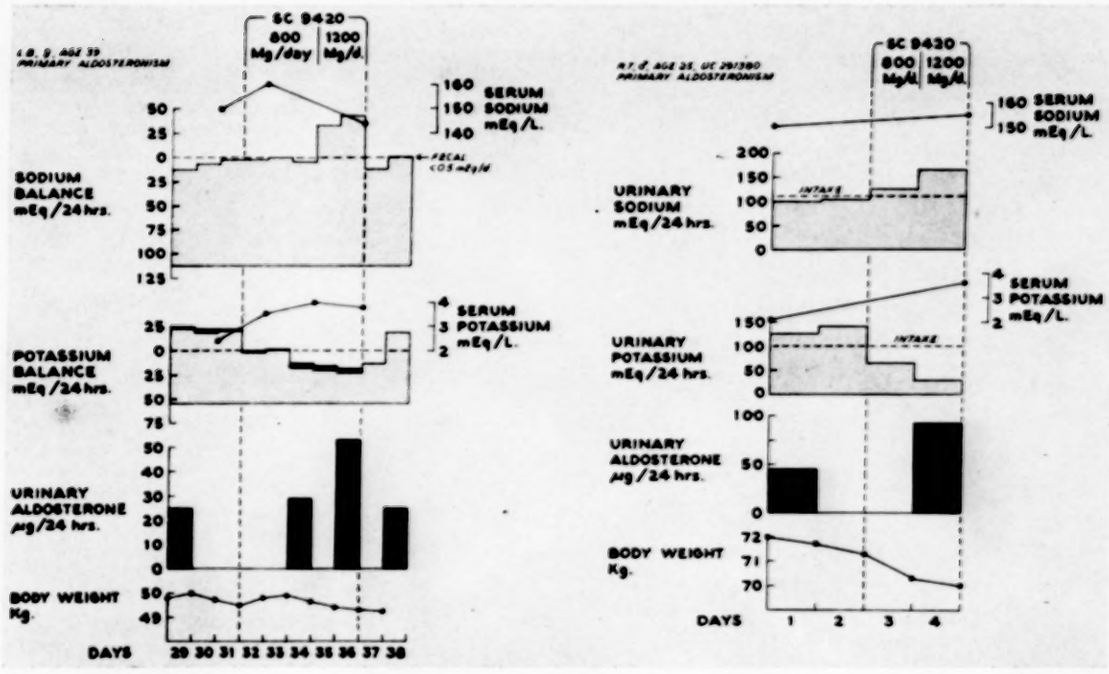

FIG. 5. Effect of spirolactone on sodium and potassium balance, serum electrolyte levels, urinary aldosterone excretion and body weight in L. B. (Case I) and R. T. (Case II).

content decreased from 33 to 28 mM per L. The addition of 200 mEq. of potassium (as KCl) daily for four days during the period of continued low salt intake resulted in a further increase of serum potassium to 4.3 mEq. per L. and a decrease in carbon dioxide content to 24 mM per L. The urinary pH rose from 6.8 to 7.4. Cumulative four day sodium excretion was 264 mEq. and cumulative potassium retention was 679 mEq. No significant changes occurred in hematocrit, serum sodium concentration or body weight during this period. Urinary aldosterone excretion rose to 85 µg. per twenty-four hours (control value 29 µg. per twenty-four hours).

Aldosterone inhibitors (*Fig. 5*): In Case I oral administration of 800 mg. of spirolactone SC-9420* daily for three days had no effect on sodium balance, but sharply reduced urinary excretion of potassium. Administration of 1,200 mg. per day for two days resulted in a sodium diuresis of 72 mEq. and a loss of 0.5 kg. in weight. Urinary aldosterone excretion increased to 53 µg. per twenty-four hours (control value 29 µg.). Serum potassium rose to 3.8 mEq. per L. (control value 2.3 mEq.); the five day cumulative potassium retention was 51 mEq. This effect quickly disappeared, and the urinary excretion of sodium, potassium and aldosterone returned to control levels. Serum potassium had fallen to 2.8 four days after SC-9420 therapy was discontinued.

In Case II administration of 800 mg. and 1,200 mg. of SC-9420 on two consecutive days produced similar responses. Serum potassium rose to 3.6 mEq. per L. (control value 2.1 mEq.) and urinary aldosterone excretion increased to 90 µg. per twenty-four hours (control value 45 µg.).

Response to Human Growth Hormone (*Fig. 6*). In Case I intramuscular injection of 4.1 mg. of human growth hormone* at 8 A.M. and 12 noon on the experimental day resulted in retention of 87 mEq. of sodium, slight amounts of potassium, and 1.6 gm. of nitrogen. During the first twelve hour period, urinary aldosterone excretion was not increased; during the second twelve hour period it actually decreased (from a control value of 30 µg. to 9 µg.). Eight hour endogenous creatinine clearances showed little change from control values, except for a slight rise during the period of maximum sodium retention.

In Case II maximum retention of sodium was delayed twenty-four hours and reached 79 mEq.

* Kindly supplied by Dr. C. L. Grant of Searle & Company, Chicago, Illinois.

* We are indebted to Dr. E. Alpert, Merck Sharp and Dohme, Philadelphia, Pennsylvania, for the supply of crystalline human growth hormone.

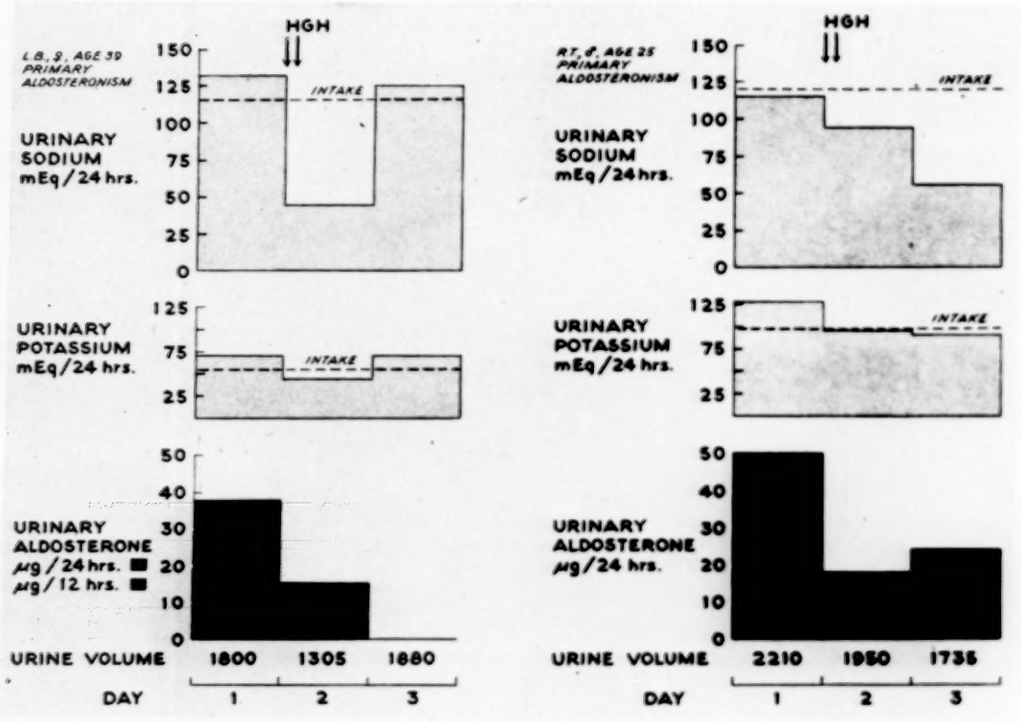

FIG. 6. Effect of intramuscular injections of 4.1 mg. of human growth hormone at 8 A.M. and 12 noon on urinary sodium, potassium and aldosterone levels in L. B. (Case I) and R. T. (Case II).

before natriuresis occurred. Twelve hour endogenous creatinine clearance rates again showed rises during the period of sodium retention. The urinary aldosterone excretion was 18 μg. per twenty-four hours (control, 50 μg.) and remained low during the retention period. Nitrogen retention of 1.2 gm. also occurred. No changes in serum electrolytes were observed in either case during the study.

Postoperative Measurements. In Case I the aldosterone content of the left adrenal gland was 0.7 μg. and of the adrenal adenoma 1.6 μg. per gm. The concentration of aldosterone in the adrenal vein plasma was 0.7 μg. per ml. In Case II adrenal vein plasma aldosterone was 0.2 μg. per ml. This contrasts with two cases of Cushing's syndrome with adrenal hyperplasia showing 0.05 μg. per ml. The urinary 17-hydroxycorticoid excretion was increased after the operation but gradually returned to control levels within four days. Urinary aldosterone was less than 5 μg. per twenty-four hours in both patients on the first postoperative day, but it promptly rose during the next seven days to values of 30 μg. per twenty-four hours in Case I whose intake of sodium was restricted.

Measurements of the ECF were repeated six weeks after the operation in Case I and eight weeks later in Case II under the same metabolic conditions. As shown in Table III, the ECF, the total blood volume and plasma volume were

TABLE III
POSTOPERATIVE MEASUREMENTS OF EXTRACELLULAR FLUID COMPARTMENTS IN L. B. (CASE I) AND R. T. (CASE II)

Compartment	Observed (L.)	Predicted (L.)	Deviation (%)
Case I			
Total blood volume	3.95	3.50	+12
Plasma volume	2.75	1.97	+39
Red cell volume	1.20	1.53	−25
Extracellular fluid (inulin)	10.6	8.3	+28
Case II			
Total blood volume	5.08	5.15	− 1
Plasma volume	2.94	2.95	0
Red cell volume	2.14	2.20	− 3
Extracellular fluid (inulin)	12.0	12.2	− 1

greatly reduced in both patients and were normal in Case II. The exchangeable Na^{22} content in Case I and Case II, respectively, was now 32 and 35 mEq. per kg. body weight. In Case I the serum electrolytes were: sodium 138 mEq. and potassium 4.5 mEq. per L. In Case II serum electrolytes were: sodium 139 mEq. and potassium 5 mEq. per L. Urinary aldosterone values remained below 5 μg. per twenty-four hours in both subjects six weeks after surgical operation.

Rapid infusion of the same 0.9 per cent saline loads under comparable conditions failed to show the previous natriuresis, diuresis, or rise in GFR in either patient. (Fig. 3.) The solute-free water clearance rose from 0.5 to 5.3 ml. per minute during the infusion in both patients. Now, the maximum natriuresis occurred *after* completion of the infusion. Of the infused sodium, 9 per cent in Case I and 5 per cent in Case II were excreted during the infusion, and in both patients less than 25 per cent of the infused sodium had appeared in the urine two and a half hours after the infusion.

Infusion of 750 ml. of Plasmanate also resulted in responses identical with those observed before operation. There were no changes in total blood volume, plasma volume or red cell volume twenty-four hours after the infusion but sodium retention of 54.6 mEq. in Case I and 54.4 mEq. in Case II had occurred.

COMMENTS

In both patients ECF and plasma volume were expanded to the same extent. The validity of these determinations is enhanced by the entirely different technics used to measure essentially the same compartments. Thus the chronic and excessive endogenous secretion of aldosterone in primary aldosteronism produces an expansion of the ECF and plasma volumes that is unusual in patients without edema. After operation the expanded ECF and plasma volumes returned toward normal in both cases.* Restoration was complete in Case II. Normal total body water with a high normal ECF volume has been observed previously in one case of primary aldosteronism [*18*].

The constancy of the ECF was demonstrated by the ineffectiveness of manipulations in sodium intake that ordinarily result in expansion and contraction of fluid volume and reciprocal changes in aldosterone secretion. In two reported cases [*19*] both high and low dietary sodium intakes failed to decrease or increase urinary aldosterone levels. In contrast, in one reported case [*18*] a high sodium diet was followed by a decrease in the urinary excretion of aldosterone. In our patients, sodium loading and sodium restriction were followed by extremely rapid adjustment to the change in sodium intake. Even after sixteen days of salt deprivation, return to a high salt intake failed to demonstrate any sodium retention or change in aldosterone secretion. Fixation of the ECF had apparently been achieved.

The administration of DCA in both patients and of *dl*-aldosterone-21-monoacetate to L. B. (Case I), in dosages calculated to be equivalent in sodium-retaining potency to their daily endogenous secretion of aldosterone, failed to effect any further increase in their expanded state. Sodium balance, weight and the negative potassium balance were little changed. This refractoriness to sodium-retaining hormones is not a consequence of potassium depletion since the administration of DCA to potassium-depleted normal subjects has been shown to increase further the negative potassium balance and produce marked sodium retention [*20*].

The results of rapid infusion of 0.9 per cent saline solution corroborated these observations of the constancy of the expanded state. A decrease in aldosterone secretion could not be responsible for the sodium loss in these cases. Curiously, in the syndrome of autonomic insufficiency [*21*], the response to rapid sodium loading appears to be identical with that observed in our two cases. Here, however, aldosterone secretion is lower than normal [*22*], and the response unaltered by large or continued doses of salt-retaining steroids. In both of these conditions the increased GFR may be the most important factor in the excessive sodium excretion following rapid sodium loading. This pattern of response in primary aldosteronism could well be the effect of an increased blood volume and ECF on the autonomic regulation of circulatory dynamics. The compensatory rise in GFR may explain the lack of edema in these patients. Once the lability of the glomerular filtration is lost, as in renal disease or heart failure, progressive sodium retention and edema will occur.

The urinary excretion of sodium following rapid salt infusion was found to be augmented in Cushing's syndrome [*23*], hypertension [*24*],

* The decrease in red cell volume in Case I may be the consequence of blood loss during surgery.

previously hydrated normal subjects [*25*] and patients with intrathoracic tumors with sodium loss and inappropriate antidiuretic hormone secretion [*26*]. The increased excretion of salt loads occurred without significant changes in GFR in all but the latter, in which it was not measured, in contrast to the elevation observed in the two cases herein described.

After operation in the two patients (Cases I and II), when the expanded ECF and hypervolemia had returned toward normal values, a considerably lower basal GFR was observed. The responses in both patients to the same 0.9 per cent saline loads under the same conditions were now normal. The blood pressure was 160/90 mm. Hg in Case I and 180 to 190/110 to 120 mm. Hg in Case II at this time, and did not rise, nor did the previously exaggerated increase in GFR occur. It would appear unlikely that the normal response after operation is a consequence of a fall in blood pressure, as has been suggested [*27*]; it is more likely to be related to the failure of the GFR to rise significantly in the presence of a normal ECF volume.

Phlebotomy produced a marked increase in urinary aldosterone, comparable to that seen in normal subjects [*28*]. The observation of very low urinary levels of aldosterone immediately after surgery, below 5 μg. per twenty-four hours with still elevated urinary 17-hydroxycorticoids on the first postoperative day, suggests that there may be suppression of aldosterone secretion by normal tissue without histologic evidence of atrophy. Thus the response to phlebotomy may be related primarily to the tumor. Infusion of Plasmanate produced a decrease in urinary aldosterone to one-third that of the control day, similar to the response of normal subjects receiving hyperoncotic albumin [*28*].

The changes in urinary aldosterone induced by phlebotomy and plasma infusion suggest that these aldosterone-producing tumors were indeed subject to physiologic control. This, however, could not be demonstrated on different sodium intakes. The transient natriuresis during the first four-hour period after Plasmanate infusion suggests that similar mechanisms may have been operative. However, the continued osmotic activity of plasma proteins presumably accounts for the subsequent retention observed.

Spirolactones inhibit the renal effects of aldosterone [*29*]. With the administration of large doses of SC-9420 the peripheral effects of aldosterone were blocked and natriuresis and weight loss followed. The consequent loss of ECF may have been the effective stimulus to increased aldosterone secretion, as reflected in the observed rise in urinary aldosterone. Our results in this respect are similar to those of others [*30,31*]. The increase in urinary aldosterone is probably not due to the slight potassium retention or increase in serum potassium that occurred, for on a salt-restricted diet (days five through twelve, Fig. 1) patient L. B. retained approximately the same level (3.3 vs. 3.8 mEq. per L.) with essentially no increase in urinary aldosterone.

Aldosterone secretion of these adenomas was further altered by procedures not effecting changes of ECF. (Table II.) In Case I and Case II, aldosterone secretion was increased following intravenous administration of adrenocorticotropin, as has been observed previously [*18,32*].

Administration of an adrenocortical 11-β-hydroxylase inhibitor, SU-4885, led to a marked decrease in urinary aldosterone in Case II. This may well represent inhibition of aldosterone synthesis, as has been previously observed [*33*]. The results are more difficult to interpret in Case I. If the rise in aldosterone excretion during the second twelve hour period represents a response to endogenous ACTH, then the lack of a rise during the first twelve hour period, when stimulation by endogenous ACTH must also have been present, suggests partial inhibition of synthesis.

Potassium depletion in normal subjects blunts the response to sodium restriction, and decreases in urinary aldosterone occur despite continuing sodium restriction [*22,34*]. This phenomenon may make abnormally high aldosterone values decline to normal levels. The marked difference in urinary aldosterone between the state of potassium depletion and the partially potassium-replenished state in Case I suggests that the mechanisms inhibiting aldosterone secretion in potassium-depleted normal subjects are probably operative. Thus an increased aldosterone excretion in the potassium-replenished state may well reflect the true secretory potential of the adenoma and not primary stimulation by potassium administration.

Human growth hormone, reported to have increased aldosterone secretion and sodium retention in patients with hypopituitarism [*35*] but not in normal subjects [*36,37*], caused marked sodium and fluid retention but a decrease in urinary aldosterone. The resultant

ECF expansion probably explains the fall in urinary aldosterone during the period of fluid retention. The absence of a rise in aldosterone and the failure to respond to exogenous aldosterone or to large doses of DCA suggests that the sodium retention produced by growth hormone is not mediated by the salt-retaining steroids. This conclusion is supported by the demonstration of sodium retention following administration of human growth hormone in a bilaterally adrenalectomized patient [*36*] and of bovine growth hormone in adrenalectomized rats [*38*].

SUMMARY

Two patients with primary aldosteronism, accompanied by hypertension, hypernatremic, hypokalemic alkalosis and severe potassium depletion, were demonstrated to have an increased volume of extracellular fluid. A marked rise in plasma volume without any change in red cell volume was observed. Changes in sodium intake failed to alter the expanded state. Only minimal responses to salt-retaining hormones were present. Rapid infusion of isotonic saline solution produced a rapid rise in the filtered load, with rapid excretion of sodium and maintenance of the status quo in aldosterone secretion. The rapid changes in glomerular filtration rate appear to be a factor in limiting further increases of this chronically expanded state and would explain, in part at least, the lack of edema observed in these patients. In contrast, the tumors were shown to respond to changes in plasma volume, corticotropin, SU-4885 and spirolactone, thus demonstrating their physiologic responsiveness to uncompensated stimuli. Growth hormone was shown to have a sodium-retaining action independent of aldosterone secretion.

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Reviews

Occlusive Cerebrovascular Disease*

Pathogenesis and Treatment

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It has been estimated that there are two million people suffering from vascular disease of the brain in the United States [*29*] and that 60,000 people die of cerebrovascular disease annually in the United Kingdom, which has a population slightly over one-quarter that of the United States [*11*]. As our life expectancy continues to increase, it is certain that the annual mortality and morbidity from cerebrovascular disease will continue to grow.

This communication will be confined to practical aspects of clinical diagnosis in cases of stroke, the nature of production of cerebrovascular symptoms and the treatment of patients suffering from occlusive vascular disease. The problem of intracranial hemorrhage is an important one, but will not be discussed here.

The Genesis of Occlusive Cerebrovascular Disease. It should be stated at the outset that cerebrovascular symptoms are produced by the combination of structural changes in cerebral vessels (the anatomical substratum of occlusive cerebrovascular disease listed in Table 1) and physiological changes best termed "hemodynamic crises" that account for the production and any reversibility of symptoms. These circulatory changes, such as fall in blood pressure, platelet embolism or decreased cardiac output, can often be recognized only in the living patient and constitute one of the reasons why an occluded vessel may not be found in the brain at necropsy despite cerebral softening [*8*] and why a patient dying with severe neurological signs may only show patchy softening of the brain with insufficient anatomical damage to account for the functional deficit present during life. Another reason why the pathologist fails to find the occluded or narrowed vessel is that certain common sites of atherosclerotic and stenotic change of the cerebral vessels are rarely examined at necropsy because they are inaccessible (such as the cervical portion of vertebral arteries) or because their dissection and removal (as in the case of the carotid arteries in the neck), prevents

TABLE 1
ANATOMICAL SUBSTRATUM OF OCCLUSIVE CEREBROVASCULAR DISEASE

1. Stenosis of cerebral arteries
   (a) Atherosclerotic plaque
   (b) Arteriosclerotic kinking
   (c) Osteophytic compression (cervical spondylosis)
   (d) External compression (brain tumor, temporal lobe herniation)
   (e) Hypertensive arteriolopathy, hypertensive encephalopathy
   (f) Thrombosed aneurysm (partial)
2. Thrombosis of cerebral arteries
   (a) Atherosclerosis of internal carotid artery
   (b) Atherosclerosis of vertebral-basilar arterial system
   (c) Atherosclerosis of smaller cerebral vessels
   (d) Thrombosis of vessel due to saccular aneurysm
   (e) Inflammation of vasa vasorum of large vessels and arteritis of small cerebral vessels (syphilis, polyarteritis nodosa, disseminated lupus, giant cell arteritis, temporal arteritis, pulseless disease)
3. Embolism of cerebral arteries
   (a) Fragmentation of mural thrombus on plaque of proximal cerebral vessel (carotid and vertebral arteries)
   (b) From heart (rheumatic heart disease, subacute bacterial endocarditis, mural thrombus after myocardial infarction)
4. Occlusion and stenosis of cerebral vessels due to disease of the aortic arch (aortic arch syndrome, dissecting aneurysm of aortic arch)
5. Venous thrombosis (cortical thrombophlebitis, postpartum and marantic phlebothrombosis

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satisfactory embalming of the head and neck by the undertaker. In a smaller proportion of cases the occlusive process may be as far removed from the brain as the subclavian artery or arch of the aorta.

For these reasons we have undertaken a systematic arteriographic study of all patients suffering from cerebrovascular disease admitted to the Detroit Receiving Hospital.* This study has proved to be extremely valuable from an investigative point of view since it permits accurate diagnosis during life, knowledge of the sites and frequency of occlusive disease and objective evaluation of therapy. The surviving patients are then followed up in our clinic. Every effort is made to obtain full autopsy examination in patients who die.

Arteriographic evaluation of cases of stroke has not proved to be hazardous in our hands. Arteriography is always performed under local anesthesia, and sodium diatrizoate (Hypaque®) † or diatrizoate and methyl glucamine (Renografin®) ‡ are used as contrast media. A percutaneous injection is made to both carotid arteries in the neck below the bifurcation and to both vertebral arteries and their intracranial branches after percutaneous catheterization of the brachial arteries using the Seldinger technic and a catheter guide. Arteriographic examination has now been performed in over 300 cases, and in 125 cases all four vessels (carotids and vertebrals) have been examined in the same patient.

STENOSIS OF CEREBRAL VESSELS

Atherosclerotic Plaques and Forward Embolization. Proximal stenosis and occlusion of the vertebral-basilar and carotid arterial systems accounted for approximately one-third each of cases of stroke, and the remaining one-third consisted of "small vessel disease," by which is meant occlusive disease of the middle, anterior and posterior cerebral arteries and their branches [*22*].

We have now collected three cases (one with autopsy) in which serial arteriograms before and after dicumarol therapy have shown a reduction in size of the stenosing lesion in the neck. One such case will be summarized briefly.

A. B., a thirty-eight year old man with hypertension, noted difficulty in walking twenty-four hours prior to admission. On the day of admission, while working at a machine, he signaled to a work-mate to turn the machine off. He began to drool from the right side of his mouth, his right side became weak, and he collapsed. On admission he was comatose. Later, aphasia, apraxia, right hemiplegia and bilateral extensor plantar reflexes were noted. An electroencephalogram showed a left temporal slow wave focus, and the cerebrospinal fluid contained 100 erythrocytes and 20 leukocytes per cu. mm. with a total protein of 60 mg. per cent. A left carotid arteriogram (Fig. 1A) showed narrowing and irregularity of the origin of the internal carotid artery due to a plaque with a mural thrombus measuring 2 cm. in length. Digital compression of the right carotid artery produced syncope. The patient was treated with heparin and dicumarol and rapidly improved. Serial electrocephalograms showed improvement of the left temporal focus. After two weeks of anticoagulant therapy, which resulted in improvement, left carotid arteriography was repeated and the filling defect due to the plaque and mural thrombus was definitely reduced in size. (Fig. 1B.) Anticoagulant therapy was discontinued because of bleeding at the site of a muscle biopsy (for possible collagen disease). Shortly thereafter the patient suffered a fatal complete thrombosis of the left internal carotid. At autopsy, a small plaque of the internal carotid artery at the bifurcation was noted, with a fresh, soft thrombus superimposed upon it which occluded the entire vessel.

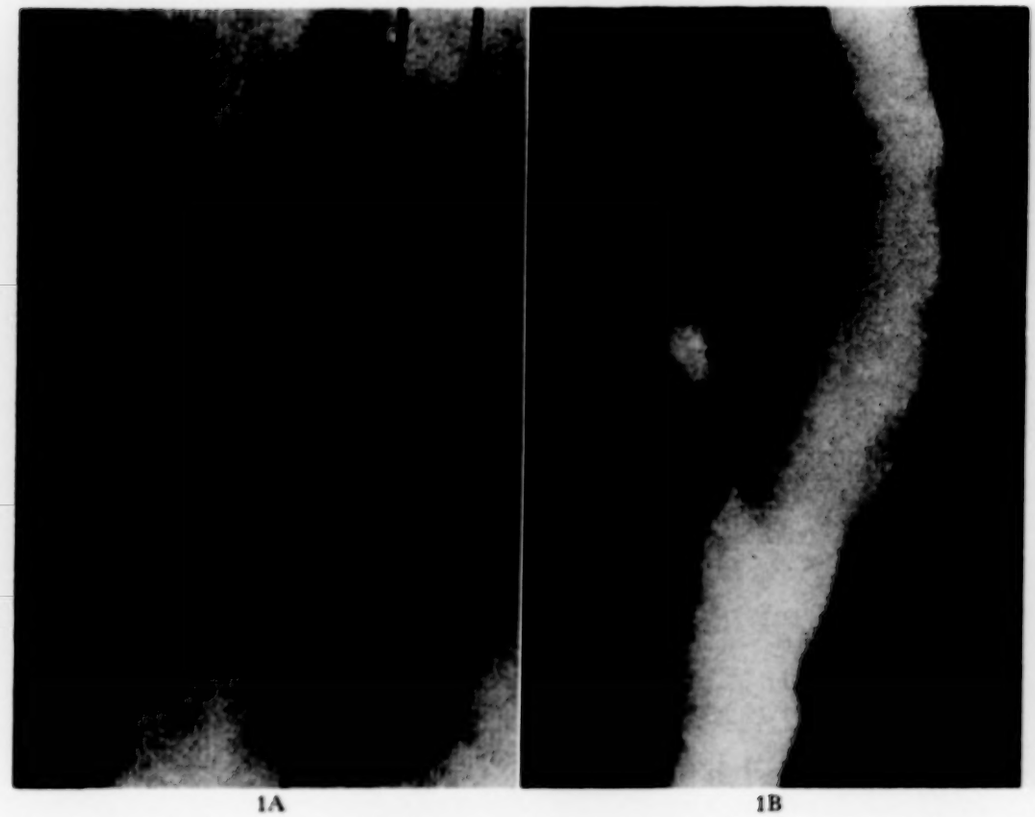
It is quite evident from the serial arteriograms and the autopsy findings in this case that at the time of onset of this man's symptoms an atherosclerotic plaque with superimposed mural thrombus was present in the left internal carotid at the carotid sinus in the neck. The pathogenesis of symptoms and the probable effects of therapy in this case are schematically represented in Figure 2. Such platelet embolization of distal cerebral vessels arising from proximal occlusive disease has also been photographed in experimental animals [*5*], and from Fisher's description [*6*] appears to have been observed in the retina of a patient suffering from proximal occlusive disease of the carotid artery.

From necropsy and arteriographic studies, the same process of atherosclerotic stenosis, mural thrombosis and embolism to vessels supplying the brain-stem, cerebellum and occipital lobes undoubtedly occurs in the vertebral arteries in the neck [*19,28*]. Such atherosclerotic plaque formation appears at certain sites of predilection in the vertebral-basilar system. The most common sites are the basilar artery, the intracranial portion of the vertebral arteries and the origin of the vertebral arteries from the subclavian arteries [*28*]. Atherosclerosis (as distinct from

* Arteriographic examination has been performed by my colleagues Dr. Sheila Sheehan and Dr. Raymond Bauer.

† Supplied by Winthrop Laboratories, New York, New York.

‡ Supplied by the Squibb Institute for Medical Research, New York, New York.



1A 1B

FIG. 1. Case A. B. Arteriograms of the bifurcation of left common carotid artery. The internal carotid artery is outlined in black ink. A, arteriogram taken shortly after admission shows a large filling defect (outlined with black dots) at the origin of the internal carotid artery. B, repeat arteriogram made two weeks after anticoagulant therapy (heparin and dicumarol) to show reduction in size of filling defect.

arteriosclerosis) of the second portion of the vertebral artery is rare in the absence of cervical spondylosis [*9*]. Cervical spondylosis is a common disease which affects subjects of the same age in whom atherosclerosis and arteriosclerosis are common. The vertebral arteries as they pass through the transverse foramina in the neck are frequently compressed by the osteophytes of cervical spondylosis. (Fig. 3.) In such patients symptoms are commonly provoked by rotation of the neck, which stretches or compresses the vertebral arteries as they pass through the transverse foramina, and intensify the stenosis. Atherosclerosis also tends to occur at the sites of compression, probably due to the vascular damage, and complete occlusion may result [*9,28*].

Not all patients with proved cerebral atherosclerosis have elevated serum cholesterol levels, although it is possible that hypercholesterolemia may have been present earlier [*22*]. On the basis of clinical evidence, there is no doubt however, that cerebral and coronary atherosclerosis are more common in subjects with hypertension, diabetes and in conditions known to be associated with hypercholesterolemia, such as myxedema and familial hypercholesterolemia. Furthermore, careful investigation of subjects with symptomatic cerebrovascular disease will show associated myocardial damage due to atherosclerosis of the coronary arteries in about 60 per cent [*18*].

Arteriosclerotic Kinking. We use the term arteriosclerosis (in contrast to atherosclerosis) to mean a more diffuse degenerative change of the arterial wall, with fibrosis but without atherosclerotic plaque formation. The cerebral arteries become widened and elongated, and have a characteristic angiographic appearance. Lengthening of the vessels may result in extreme tortuosity, which may become so marked in the arteries of the neck that the vessel may loop upon them in a circular manner and intermittent obstruction may result from kinking. (Fig. 4.) In one case, Dr. Herbert Robb, working in col-

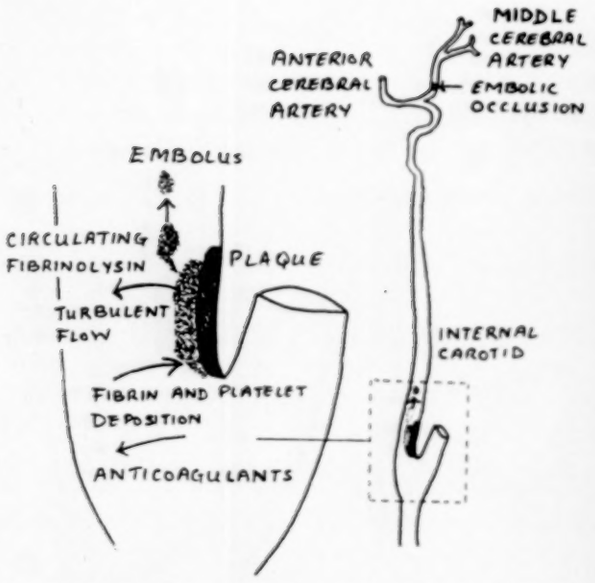


FIG. 2. Schematic diagram to show possible pathogenesis of forward embolization from atherosclerotic plaques of the major cerebral vessels in the neck. The diagram is based on correlation of clinical, necropsy and arteriographic data (Fig. 1) of Case A. B. An atherosclerotic plaque may be the site of fibrin and platelet deposition in the zones of turbulent flow around the plaque. These may fragment and cause embolization of the distal cerebral arteries.

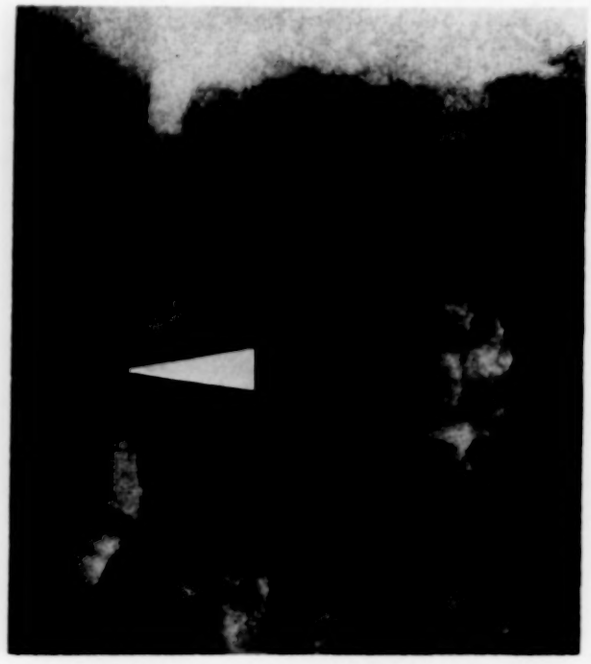


FIG. 3. Vertebral arteriogram to show displacement of the vertebral artery in the neck by the osteophytes of cervical spondylosis. Compression of the vertebral artery by the osteophyte may result from rotation or hyperextension of the neck.

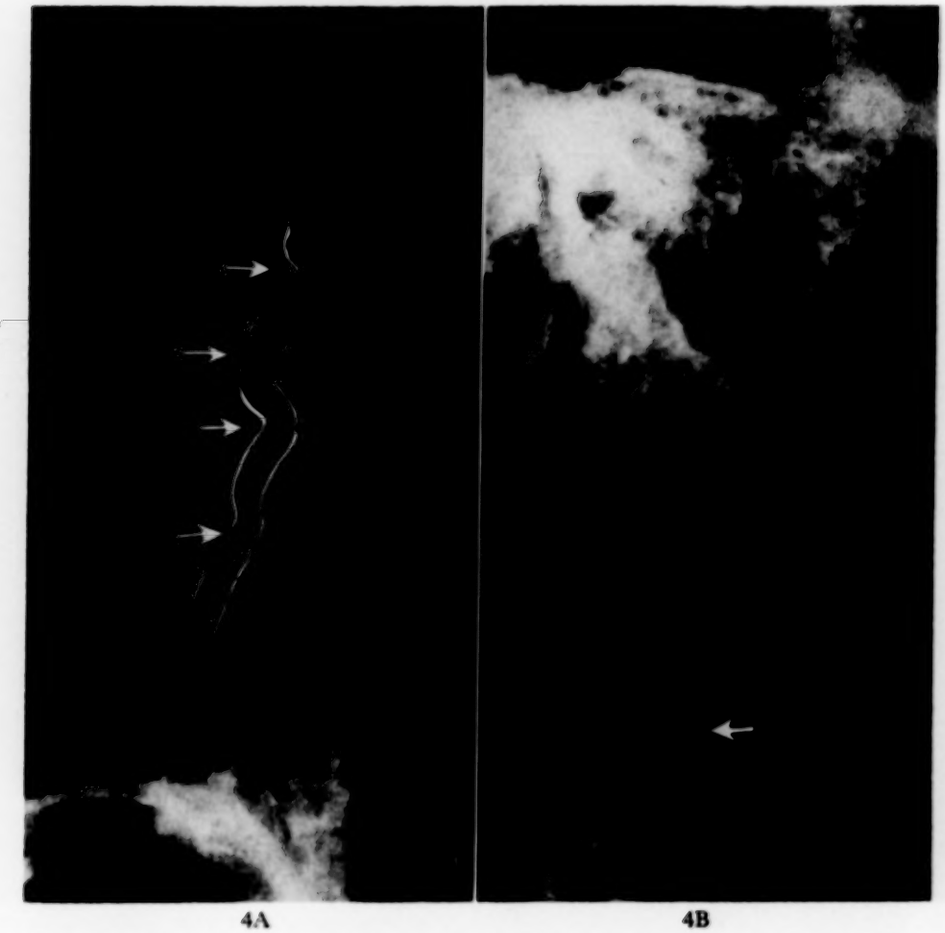
laboration with our service, has demonstrated that this may be a (rare) cause of recurrent symptoms of cerebral ischemia since, following surgical resection of a length of the redundant vessel with end-to-end anastomosis, there have been no further cerebral symptoms.

Rarely, in large firm, intracranial tumors (e.g., sphenoid wing meningioma) there may be compression of major cerebral vessels either directly or by herniation and compression of the posterior cerebral artery against the edge of the falx.

Hypertensive Arteriolopathy. In renal hypertension [*1,20,21*], and probably also in toxemias of pregnancy, acute porphyria and severe essential hypertension, there appears to be a circulating vasoconstricting agent which causes excessive irritability of the smooth muscle in the walls of small arteries. The cerebral arteries normally respond to an increase in intraluminal pressure by constricting. The retinal arteries during episodes of severe hypertension with elevation of systolic blood pressure above 200 or 250 mm. Hg may show intense spasm with retinal edema and perivascular hemorrhages. There is abundant clinical and pathologic evidence in man that the same process is present in the brain also. Experimental studies in the hypertensive rat, cat and monkey have shown that this arteriolospasm occurs diffusely throughout the brain in renal hypertension, with accompanying swelling of the brain. We have found that the intravenous injection of purified hypertensin* to the monkey produces spasm in cerebral vessels comparable to that seen in experimental renal hypertension, but it is transient and permits the recording of resulting hemodynamic effects. Associated with the rise of systolic and diastolic blood pressure there is reduction of cortical blood flow, which persists after the blood pressure has returned to normal levels. There is an increase in intracranial pressure, the cortical oxygen tension is decreased, and the electroencephalogram slows due to cortical or subcortical ischemia. The cortical carbon dioxide partial pressure is reduced since cerebral metabolism is decreased due to ischemia.

If severe hypertension is allowed to persist unchecked the intense spasm eventually results in rupture or injury to small vessels, followed by hyperplastic arteriolopathy which adds perma-

* Provided by Ciba Pharmaceutical Company, as Hypertensin-Ciba.



4A 4B

FIG. 4. Retrograde brachial catheterization and injection of the vertebral arteries in a sixty year old man to show the following: A, compression and displacement of the right vertebral artery in the neck by exostoses, at points indicated by white arrows. B, arteriosclerotic tortuosity and kinking of the left vertebral artery in the neck of the same patient. Occasionally such kinking can cause obstruction of flow to major vessels in the neck.

nent structural stenosis besides the functional spasm already mentioned.

The Question of Spasm Accompanying Aneurysmal Rupture. When an aneurysm ruptures, arteriograms performed within the first few hours of rupture show that the vessels adjacent to the ruptured vessel are narrowed, which is generally interpreted as evidence of spasm [*24,25*]. The question is not entirely settled because clot within the vessel or compression from without due to bleeding or extensive edema may compress the vessel and simulate spasm in the arteriograms. In any event, whether arterial constriction be due to these factors or to true spasm, the local reduction in cerebral blood flow may result in symptoms and probably contributes to the infarction not uncommonly seen at autopsy in the area of distribution of the vessel giving rise to the aneurysm which ruptured. It should also be remembered that thrombosis of an arterial aneurysm may occur with or without rupture and give rise to symptoms due to occlusion or stenosis of the parent vessel.

Thrombosis of Cerebral Arteries. At the present time the most common cause of thrombosis of cerebral vessels is atherosclerosis with mural plaque formation. The plaque roughens the endothelial coat of the vessel, platelets and fibrin tend to stick to the plaque, resulting in progressive enlargement due to encrustation and incorporation of the mural deposits within the plaque by organization [*3*]. The ensuing slowing of flow results in turbulence in the vicinity of the plaque, with migration of platelets toward the plaque and the formation of a platelet thrombus [*12–14*]. This process may gradually progress to

the production of intermittent arterial insufficiency or "localized cerebral claudication," and ultimately infarction will result. In such gradual thrombosis, a collateral circulation via the circle of Willis and communications between small branches of the middle, anterior and posterior cerebral arteries is developed. This process in the cerebral circulation is comparable to that of the coronary circulation. Angina does not, of course, occur during episodes of cerebral ischemia but instead there are episodes of transient functional paralysis often poorly termed "little strokes." Better terms are "intermittent insufficiency" or "transient ischemic attacks." Due to development of the collateral circulation, the final thrombosis may be unaccompanied by significant cerebral symptoms.

A much more serious catastrophe is sudden thrombosis of a major cerebral vessel superimposed on a small mural thrombus. In such instances there is insufficient time for collateral circulation to develop and some degree of cerebral infarction is certain; a fatal issue from swelling of the brain is not uncommon. This process may affect the young male. In such cases there is ischemia of the arterial wall of the thrombosed segment, including the carotid sinus, and vagal slowing of the heart may result, associated with a prolonged P-R interval in the electrocardiogram. The ascending sympathetic nerve fibers in the carotid plexus may also be rendered ischemic so that a Horner's syndrome may be present on the same side as the carotid thrombosis. The carotid artery pulse in the neck is usually reduced and a murmur may be present over the diseased or stenotic vessel. Another useful sign in carotid artery thrombosis is reduction of the bruit that is often heard over a normal carotid artery. In pinpoint stenosis of the carotid artery, a sea-gull murmur may be heard over the carotid bifurcation; in one of my patients such a murmur disappeared following endarterectomy.

Vertebral-basilar artery thrombosis often is fatal since vital centers, including the vasomotor and respiratory centers, are in the area of distribution of this vessel. Death from middle cerebral artery thrombosis does occur but is rare. In thrombosis of the anterior and posterior cerebral arteries survival can be anticipated. Syphilitic endarteritis commonly results in intimal damage to the internal carotid and basilar arteries with thrombosis; in such cases, penicillin therapy should be combined with anticoagulant therapy since a Herxheimer reaction may result in fatal cerebrovascular thrombosis [*15*]. Similar inflammatory involvement of the vasa vasorum of the aortic arch, the major cerebral vessels in the neck and occasionally of the small cerebral vessels occurs in periarteritis nodosa, disseminated lupus, giant cell arteritis, temporal arteritis and pulseless disease. In all these arteritides steroid therapy is indicated.

Embolism of Cerebral Vessels. Forward embolism from proximal plaques of the large cerebral vessels in the neck may well emerge as the most common cause of cerebral embolism but embolism of cardiac origin is commonly recognized after myocardial infarction, in chronic rheumatic heart disease, subacute bacterial endocarditis and occasionally as a complication of cardiac surgery. The diagnosis is based on the catastrophic onset of the neurologic disability, demonstration of a source of embolism or embolism elsewhere in the body. Therapy with anticoagulant drugs is directed toward prevention of further embolic episodes [*10,23*] except in subacute bacterial endocarditis when antibiotic therapy alone may be sufficient. The therapy is unlikely to affect an established embolism, however, since irreversible infarction regularly follows total ischemia or partial ischemia in which local blood flow falls below 20 per cent for longer than six to ten minutes [*13,27,30*]. If the collateral circulation maintains a circulation distal to the occlusion of greater than 20 per cent of normal, there will be functional paralysis of brain tissue with the possibility of recovery once local blood flow is restored. Unlike vascular disease of the lower extremities in which the metabolic rate of muscle and skin is extremely low when compared to the brain, restoration of anatomic continuity of a totally occluded cerebral vessel within one to two hours will not be accompanied by any functional recovery of brain function unless a collateral circulation becomes established which is sufficient to maintain viability of the nerve cells during the period of occlusion [*13,27,30*].

Atherosclerosis and giant cell arteritis of the aortic arch may result in cerebral ischemia by occluding the subclavian arteries (from which the vertebral arteries arise), the brachiocephalic trunk or the left carotid artery. Such cases are rare but their presence may be suspected when cerebral or cerebellar ischemia is combined with the absence of pulse in one or both upper extremities. I have seen two cases in which

occlusion of the subclavian artery was accompanied by cerebellar and brain-stem ischemia with cyanosis and absent pulsation in the upper left extremity. Pulseless disease is usually due to giant cell arteritis but the same syndrome is seen (rarely) in advanced atherosclerosis. In one patient with the atherosclerotic type treated at the Detroit Receiving Hospital, gangrene of both lower extremities was present, with absent pulses in the upper extremities, transient monocular blindness and eventual hemiplegia. The diagnosis may be confirmed in such cases by angiocardiography. Surgical reconstruction of the aortic arch is now a feasible procedure. Dissecting aneurysm of the aortic arch may likewise cause cerebral ischemia by involving the innominate, subclavian and carotid arteries by the dissection. Recent advances in cardiovascular surgery, with the use of hypothermia and extracorporeal circulation permit us to contempulate surgical reconstruction of the aortic arch in such cases, since in the absence of such measures, a fatal outcome can be assumed.

Cerebral Venous Thrombosis. Thrombosis of cerebral veins may result from phlebitis complicating meningitis or from a septic focus drained by the intracranial venous system such as mastoiditis and sinusitis. In such cases administration of appropriate antibiotics usually results in rapid recovery. Occasionally, cerebral phlebothrombosis may occur in the postpartum period, presumably due to the hypercoagulability of the blood occurring at this time. Spontaneous recovery with minor cortical damage is the rule. Rarely, sagittal sinus thrombosis is seen in terminally sick persons due to severe dehydration. We have used fibrinolysin and anticoagulant therapy in such cases with success, but dangers of perivenous hemorrhage must be weighed.

CLINICAL INVESTIGATION OF CASES OF "STROKE"

No apology is made for stating what must be obvious to many physicians, since as a neurologic consultant I have found that cases of "stroke" are often labeled "cerebrovascular-accident" which, of course, is not a diagnosis at all, and that these patients are then committed more or less to the care of the nursing staff without adequate clinical investigation or therapy.

A careful history is essential to reach the correct diagnosis. In general, vascular disease of the brain may have three types of onset: catastrophic (as in embolism, hemorrhage and [rarely] sudden thrombosis), progressive (as in thrombosis) or of a stuttering type (as in vascular insufficiency). Previous episodes, often transient and referable to the same area of the brain, suggest atherosclerotic stenosis with transient ischemic attacks. Accompanying symptoms are important: chest pain suggests associated myocardial infarction; abdominal pain and melena suggest gastrointestinal bleeding as the precipitating episode; cardiac irregularity, postural syncope, precipitation of the episode by coughing or straining at stool are also important from a hemodynamic point of view. The type of headache may suggest the diagnosis. In cerebral hemorrhage the headache is intense with accompanying stiffness of the neck; in carotid insufficiency, the headache is temporal and usually on the side of the ischemia, in basilar artery insufficiency, the headache is occipital or suboccipital. Inquiry should be made regarding previous transient hemiparesis, hemiparasthesias, dysphasias, transient monocular blindness (all of which occur in carotid artery insufficiency), episodic vertigo, ataxia, photopsia, hemianopsia, blindness and quadriparesis (which characterizes vertebral basilar artery insufficiency). The past medical history should provide full information regarding associated hypertension, diabetes and heart disease.

The physical examination should include a complete medical evaluation, with particular attention directed toward the cardiac and pulmonary status. Possible causes of decreased cardiac output should be assessed, and if pulmonary congestion, pneumonitis or emphysema is present this should be noted. Inspection and palpation of the skin and tongue are important since any tendency toward dehydration is of serious consequence in cerebral circulatory insufficiency. The pulses in the neck and extremities should be palpated and auscultation should include the neck and head (for carotid and vertebral bruits). The blood pressure and pulse rate should be recorded at least once daily and careful note should be made of the state of the retinal vessels.

Neurologic examination should mention the presence or absence of any stiffness of the neck (subarachnoid hemorrhage), the mental state including orientation, ability to speak, comprehend, write and calculate. In those patients in whom it is possible, the gait should be tested. Any papilledema and the state of the visual

fields should be recorded. The status of all cranial nerves, motor strength of all four extremities, the tone and coordination including any cerebellar signs should be recorded. The reflexes, including the sucking and grasp reflex, should be tested and sensation examined.

Lumbar puncture should be performed as a routine procedure unless papilledema is present, in which case a size 21 spinal needle should be used and only the contents of the manometer removed. This is sufficient for recording cerebrospinal fluid pressure, a cell count and a Pandy test. In all other patients sufficient fluid should be drawn for a serologic test for syphilis and total protein estimation. In acute cerebral infarction or hemorrhage adjacent to the meninges or ventricles the white cell count in the cerebrospinal fluid may rarely reach 2,000 per cu. mm. with a preponderance of polymorphonuclear leukocytes. Usually there are few cells. A large number of red cells indicates hemorrhagic infarction or hemorrhage.

A roentgenogram of the chest is important for noting the size of the heart, any pneumonitis that may be present, and possible primary or secondary carcinoma, since cerebral metastasis may mimic vascular disease of the brain. It is our practice to perform a routine roentgenographic examination of the cervical spine (for cervical spondylosis which may compress the vertebral arteries) and skull (which may reveal calcification of intracranial vessels or evidence of unsuspected tumor). Routine recording of the electrocardiogram is of great value for myocardial infarction or cardiac dysrhythmia is not uncommon in association with focal cerebral symptoms.

In the electroencephalogram, slow waves in the temporal region or in one hemisphere suggest insufficiency in the distribution of the internal carotid artery. In general, hyperventilation and compression of the carotid artery tend to increase or provoke such electroencephalographic abnormality. If the electroencephalogram becomes worse during carotid compression and rotation of the head, this suggests vertebral artery disease [*28*]. In general, with the exception of septic embolism and progressive infarction, serial electroencephalograms show improvement in cerebral vascular disease.

In occlusion of the carotid artery, the retinal artery pressure tends to be reduced on the side of the occlusion since the ophthalmic artery is a branch of the carotid artery. While this can be exactly measured with an ophthalmodynamometer, it is a simple matter to use compression of the globe on each side with the finger during funduscopy and observe the ease with which the retina blanches. In a state of normal circulation considerable pressure is required to abolish the retinal artery flow; in occlusion of the carotid artery or in diffuse occlusive vascular disease the retina blanches easily when the globe is compressed on the involved side (60 per cent of cases).

The complete blood count is helpful for several reasons. A high hematocrit and red count suggest polycythemia vera or secondary erythrocythemia and hemoconcentration due to dehydration. Both conditions increase the blood viscosity and predispose to cerebral thrombosis. Polymorphonuclear leukocytosis accompanies severe cerebral hemorrhage and infarction. Urinalysis may reveal diabetes, embolic infarction of the kidneys or suggest the presence of renal hypertension. The fasting blood sugar will indicate diabetes mellitus unless infarction in the region of the third and fourth ventricles has resulted in transient hyperglycemia of central origin. The blood urea nitrogen may indicate complicating renal insufficiency, and the serum cholesterol is helpful in determining any metabolic cause of atherosclerosis. Blood culture should be taken in all patients with cerebral embolism and rheumatic heart disease.

If the diagnosis is in doubt, or a surgically remedial lesion is suspected (such as atherosclerotic stenosis of the internal carotid artery in the neck or the possibility of an intracranial hematoma), angiography will usually provide a definite diagnosis. The only exceptions are a small group of cases (less than 20 per cent) in which a small cerebral vessel is occluded that cannot be recognized by angiography. Angiography should be performed under local anesthesia since general anesthesia may lower the blood pressure and produce a hemodynamic crisis with cerebral infarction. The administration of Diodrast® is contraindicated since it is irritating to the vascular endothelium. Diatrizoate is recommended since, in our hands, we have not had a single fatality ascribable to arteriography in the examination of over 300 cases of cerebrovascular disease, and complications have been approximately 4 per cent without any being serious or persistent. Such complications have usually been a few focal convulsions during carotid angiography or, rarely, a transient worsening of the neurologic

signs, with prompt recovery. In the latter event, heparin therapy is started immediately. Pneumoencephalography is contraindicated in cerebrovascular disease since hypotension commonly occurs and may result in a severe neurologic deficit.

THERAPY IN THROMBOSIS OF CEREBRAL ARTERIES

The patient with cerebral arterial thrombosis should be placed flat in bed with the head low. Either a thin pillow or none should be used. Comatose and semistuporous patients should be turned from side to side every two hours. Excessive rotation of the head should be avoided since this compresses or stretches the vertebral arteries in the neck. Areas of reddening of the skin over the heels, ankles, buttocks, shoulders and elbows are an indication of impending pressure necrosis and always indicate that the patient is not being turned frequently enough. Decubitus ulcers can almost invariably be prevented and their frequency or absence on a large service of critically ill patients can be used as a criterion of the efficiency of the nursing and medical care. Paralyzed limbs should be given full range of passive motion daily (particular attention should be given to abduction of the shoulder joint in the hemiplegic patient) since contractures and "frozen joints" can thus be prevented.

Intravenous fluids should be given for the first forty-eight hours to prevent dehydration and prevent hypoglycemia. Thereafter, if the patient is unable to swallow oral feedings (this is generally limited to patients with infarction of the brain-stem), nasogastric feeding is maintained in small 200 ml. aliquots every two hours. Frequent small feedings do not result in regurgitation and aspiration.

Optimum blood pressure should be maintained. If shock is present, blood transfusion and norepinephrine should be given since the most important single factor in maintaining the cerebral circulation is the cardiac output. In formerly hypertensive persons whose blood pressure has fallen to normal levels, and in those subjects with intermittent heart block, ephedrine administered in doses of 25 to 50 mg. three or four times daily is prescribed. Occasionally, in severe hypertension, transient neurologic symptoms occur due to spasm of cerebral vessels [*20,21*]. The systolic blood pressure should be cautiously lowered to approximately 180 mm. Hg. This will promptly result in recovery from focal neurologic signs due to excessive hypertension and those due to hypertensive encephalopathy in which headache and papilledema may simulate brain tumor. At the Detroit Receiving Hospital we have found therapy with reserpine, Diuril® and Apresoline®, together with bed rest and barbiturate sedation, effective. Occasionally, heart failure may precipitate signs of cerebral vascular thrombosis in which case digitalis therapy is indicated. Auricular fibrillation and other cardiac dysrhythmias may also precipitate thrombosis of cerebral vessels. In such instances improved cardiac output resulting from the use of quinidine and procaine amide may reverse the unfavorable series of events. In cases of cerebral thrombosis precipitated by blood loss (surgery, gastrointestinal hemorrhage), blood transfusion and prevention of further bleeding are essential.

If cerebral infarction is severe, oxygen therapy with the intermittent use of 5 per cent carbon dioxide is indicated. This treatment during electroencephalographic recording has shown improvement in the electroencephalographic abnormality while the carbon dioxide and oxygen mixture was inhaled [*18*]. The oxygen tends to decrease cerebral anoxia and the carbon dioxide increases cerebral blood flow. Carbon dioxide may be given intermittently since some patients complain of respiratory discomfort after prolonged breathing of carbon dioxide and oxygen.

Incontinent patients require sterile indwelling catheters and bowel care since dampness and infection predispose to the formation of decubitus ulcers. Great care should be exercised to prevent infection of the urinary tract. This common complication can be avoided if the catheters, their connections and urinary drainage bottles are kept sterile and appropriate antibiotics are used at the first appearance of pyuria.

The use of anticoagulant plus fibrinolysin therapy in cerebral arterial thrombosis will be discussed later in connection with its use in the treatment of episodic cerebrovascular insufficiency.

TREATMENT OF EPISODIC CEREBROVASCULAR INSUFFICIENCY

Superimposed on the anatomic stenosis or occlusion of cerebral vessels is the probability of physiologic changes best termed "hemodynamic crises" [*4*] which produce episodes of

cerebrovascular insufficiency or thrombosis. Recently, by means of arteriography, we have come to recognize forward embolism from proximal plaques in the large cerebral vessels as a cause of intermittent cerebral episodes. Resection of the plaque or long-term anticoagulant therapy appear to be beneficial forms of therapy. As already mentioned, hemodynamic crisis may be precipitated also by excessive rotation or hyperextension of the neck [*28*], due to compression and stenosis of the vertebral arteries in the neck particularly if cervical spondylosis with exostoses is present; and advanced arteriosclerosis with extreme tortuosity and kinking of either the vertebral and carotid arteries in the neck. (Fig. 4.)

In our experience the most common form of hemodynamic crisis, however, is due to a fall in blood pressure, sometimes resulting from the unwise use of hypotensive drugs in the hypertensive patient, or to postural hypotension particularly in diabetic subjects. Simply discontinuing the use of hypotensive drugs, or giving ephedrine sulfate (25 to 50 mg. three to four times daily) may abolish or minimize the attacks. In addition to the administration of sympathomimetic drugs, weight reduction and increasing muscle tone by exercise may abolish postural hypotension. Carotid sinus sensitivity may rarely produce episodic cerebrovascular insufficiency, particularly in subjects with carotid stenosis or occlusion in whom sinus sensitivity is extremely common. Atropine is of some value but surgical denervation or resection of the sinus, if the vessel is completely thrombosed, may terminate the episodes. Excessive blood loss should be avoided, particularly if the subject with cerebrovascular disease is undergoing surgery. Lumbosacral sympathectomy should also be avoided in such persons and precautions should be taken in allowing patients to stand for the first time after reconstruction of atherosclerotic iliac and femoral arteries.

Convulsive disorder occasionally accompanies cerebrovascular disease, particularly in hemorrhagic infarction and atherosclerosis of small cerebral vessels such as occurs in diabetes. The cerebral metabolic rate is greatly increased in epilepsy and episodic hemiplegia may follow each convulsion in subjects with cerebrovascular disease [*17*]. In such subjects anticonvulsant therapy may abolish the attacks. In atherosclerotic diabetic subjects receiving insulin therapy, hypoglycemia may precipitate focal neurologic signs which are usually promptly relieved by the administration of glucose [*16*].

INDICATIONS AND CONTRAINDICATIONS OF ANTICOAGULANT THERAPY

Once cerebral infarction has occurred with tissue necrosis, restoration of blood flow to the damaged area by either medical or surgical means will not restore function. The ideal situation for treatment is one in which ischemia has provoked minimal symptoms and the collateral blood flow is sufficient to maintain viability but not function of tissue. In this situation return of flow will restore normal function and relieve symptoms.

There is evidence, both clinically [*10,18,23*] and experimentally [*12*], that anticoagulant therapy with heparin in the acute stages and dicumarol for long-term purposes is useful in occlusive cerebrovascular disease. The theoretic basis for such therapy is to reduce the incidence of forward embolization from proximal plaques of the cerebral vessels in the neck. Such platelet deposition and platelet thrombosis is a striking feature of experimental cerebral thrombosis [*12*]. Anticoagulant drugs also appear to prevent adhesiveness of the blood elements, which increases in zones of slowed flow. Neither heparin nor dicumarol can dissolve a fibrin clot; once it has formed, this requires fibrinolysin which is present normally in small amounts in the circulating blood. We are presently investigating the intravenous use of fibrinolysin in addition to anticoagulant drugs as a therapeutic measure in cerebrovascular thrombosis. Our preliminary results in fifty cases would indicate that this treatment is feasible, is not unduly hazardous, has not resulted in cerebral hemorrhage and was in the series evaluated.

Experience with anticoagulant therapy in cerebrovascular disease indicates that there are several important contraindications to this form of therapy. Obviously, suspicion of intracerebral or intracranial bleeding is a contraindication, as are potential sites of bleeding elsewhere, such as the presence of peptic ulcer or recent abdominal surgery. Severe liver disease is a contraindication since small doses of dicumarol may further interfere with an already deficient prothrombin mechanism. It has been our practice to lower the blood pressure of severely hypertensive patients to a systolic blood pressure of approximately 180 mm. Hg prior to anticoagulant therapy because of the known tendency of severe

hypertension to produce hemorrhagic infarcts in the brain. Xanthochromia of the cerebrospinal fluid and the presence of erythrocytes in excess of 3,000 per cu. mm. (excluding traumatic tap) has arbitrarily been taken by us as a contraindication to anticoagulant therapy.

It is imperative that the patient return twice monthly for prothrombin determinations when long-term anticoagulant care is undertaken. Unreliable, demented and uncooperative patients should therefore not receive anticoagulant therapy unless they are under close supervision. Occasionally, in the elderly patient an unpredictable response to dicumarol is encountered, for unknown reasons. In such cases vitamin K is given, and if this abnormal response occurs repeatedly after fair therapeutic trial, anticoagulant therapy must be abandoned.

CONCLUSIONS

The considerable advances made in the past decade in the medical and surgical treatment of occlusive cerebrovascular disease justify careful evaluation of each case of "stroke" and permit definitive diagnosis by arteriography if the diagnosis is in doubt or if surgical therapy is considered feasible. In atherosclerotic subjects, rapid reduction of blood pressure and other causes of hemodynamic crises, as herein described, should be avoided. In some patients, the use of anticoagulant drugs and fibrinolytic agents should be attempted; in other patients, such therapy is contraindicated.

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Chronic Pyelonephritis*

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It has been said that chronic pyelonephritis can be recognized much more often at autopsy than during life. If this statement is true, there must exist a large number of cases of "inapparent pyelonephritis." It has been suggested that these cases can be detected by refined laboratory methods, particularly by quantitative bacteriologic analyses of the urine [*1,2*]. This concept contributed much to the renewed interest in this disease in recent years.

We reviewed both the literature and our own material in order to gain a clearer insight into the reliability of our diagnoses. Much of this study is devoted to a consideration of the morphologic aspects of chronic pyelonephritis. Many conclusions concerning pathogenesis, treatment, complications and sequelae of any disease depend on accurate identification of the disorder by morphologic means. On this, in turn, depends ultimately the evaluation of clinical signs and symptoms.

Pyelonephritis may be defined as an infectious disease of the kidney characterized by a direct inflammatory reaction of the pelvis and parenchymal interstices to invading organisms, with secondary effects on the tubular, vascular and glomerular apparatus. This concept is derived from what we know about the acute and subacute phases of this disease, but whether or not it can be applied to all cases now categorized as chronic pyelonephritis is by no means certain. It has been stated [*3*], and often repeated, that a history of acute pyelonephritis is rare in chronic advanced pyelonephritis. Because of this, and in the face of a multitude of more or less nonspecific clinical and anatomic criteria, the identification of many cases of scarred kidneys as pyelonephritis remains questionable. The final judgment too often depends on the subjective evaluation of a total pattern, which may be very variable.

A review of the literature on subacute and chronic pyelonephritis leaves the impression that the criteria set down in the classical investigations of Staemmler and Dopheide [*4*] and Weiss and Parker [*5,6*] have been generally accepted. Indeed, we seem so sure of the morphologic characteristics that an atmosphere of complacency has descended upon us. This confidence is reflected in numerous statistics based purely on findings at autopsy [*3,7–13*], irrespective of the availability of corroborative bacteriologic or clinical findings, including persistent or recurrent pyuria or other signs and symptoms.

Follow-up studies over long periods are often talked about but less frequently documented. Some investigators have shown that the likelihood of permanent damage increases with persistent pyelonephritis in childhood [*14–17*], and many individual cases of recurrent attacks have been reported to result in chronic pyelonephritis or advanced renal contraction. We know, however, that most cases of acute pyelonephritis are limited in their progression [*5,18*]. We do not know, except by inference, how often, under what circumstances, and by what mechanisms the initial acute disease may advance through various stages. In fact, the pathogenesis of chronic, non-obstructive pyelonephritis is so obscure that the existence of a non-infectious chronic pyelonephritis has been postulated. Weiss and Parker [*6*] presume that an inflammatory process may progress independent of infection.

The diagnoses of chronic and healed pyelonephritis are based on a composite picture of multiple criteria. Since their order of significance is controversial, we should not be surprised that statistical evaluations based on postmortem findings may vary greatly with individual observers. Whether, for instance, a decrease in the number of observed cases of pyelonephritis at

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autopsy actually occurred in Jackson's series [*10*] from 1939 to 1955, or whether different criteria were applied cannot be stated with certainty. In our own experience we have not infrequently changed our diagnoses upon restudy of our old cases.

In addition, through the years there have been major differences in observations of specific morphologic features, and the emphasis placed upon their importance. As an example, for instance, in the older literature up to 1934 vascular changes were considered to be minimal and irrelevant [*4,19*]; since the report of Weiss and Parker [*6*] most subsequent authors stress their frequency and importance. Also, the older literature emphasizes a "barrier zone" as characteristic for chronic healed pyelonephritis [*4,19,20*], whereas the modern literature does not so much as mention it.

A critical review of the morphologic features of chronic pyelonephritis therefore seems indicated. This is all the more necessary since needle biopsies have become available as a promising tool in the study of renal diseases [*3,21,22*]. Because of the patchy distribution of pyelonephritis, this technic does not lend itself readily to the investigation of this disease. Nevertheless, some microscopic features of pyelonephritis are frequently seen in combination with other kidney diseases, and it is desirable that the significance of its morphologic facets should be clearly understood and placed in proper perspective.

We have re-examined the cases classified as chronic pyelonephritis at autopsy, from the files of the Milwaukee County Hospital from 1954 through 1959, in an attempt to re-evaluate our own criteria, correlating our findings with the available clinical data. We found that the frequency with which the diagnosis of active chronic pyelonephritis was made in consecutive years did not vary significantly during this period. Also, we restudied two additional groups of cases for the purpose of comparison, namely, those classified as focal pyelonephritic scars and cases of primary vascular diseases.

MORPHOLOGIC STUDIES

A number of structural changes have been described as distinctive for pyelonephritis, and we shall attempt to analyze each of them.

Pattern of Distribution. The major criterion is the irregularity with which the process is distributed. Pyelonephritis may be unilateral, and within the one kidney may be confined to certain portions of the renal parenchyma belonging to one or more calices. Even if the entire kidney is involved, the process is characteristically patchy or, if confluent, there is irregularity in the extent and degree of involvement, as emphasized by hyperplasia of the remaining nephrons. Exceptions to this rule are found in the very early stage of diffuse purulent pyelonephritis and in a few instances of so-called healed chronic pyelonephritis in which the surface may be conspicuously smooth. Chronic pyelonephritis thus cannot be designated a diffuse disease of the renal parenchyma in the same sense as glomerulonephritis or nephrosis, for in the majority of cases it is a focal lesion of variable extension, although it may ultimately involve the entire organ by confluence. It is commonly thought that the flat broad scar is characteristic for pyelonephritic contraction if the corresponding medulla is contracted and the minor calices widened, in contradistinction to the "V" shaped deep vascular scar. We shall point out later (see p. 594) that this criterion may be fallacious, because it can be demonstrated that similar scars are commonly due to ischemia without pyelonephritis.

Nature of Inflammatory Infiltrate. The interstitial infiltrate is characteristically pleomorphic, containing lymphocytes, plasma cells, other monocytes and, depending on the stage, or if recurrent, polymorphonuclear leukocytes. It is generally accepted that an infiltrate composed solely of lymphocytes cannot be regarded as evidence of primary interstitial inflammation, for it may appear also in areas of obvious primary vascular atrophy. Plasma cells are said to be seen when a breakdown of the basement membrane occurs [*23*]. This destructive process may be the result of inflammation. But destruction of tubular basement membrane is not necessarily followed by plasma cell infiltration, since this occurs extensively in tubulorhectic nephrosis without inducing the appearance of a significant number of plasma cells. Even though the appearance of plasma cells in a mixed mononuclear infiltrate may be taken as presumptive evidence of chronic inflammation, it is not an unequivocal criterion of pyelonephritis or other forms of interstitial nephritis. Plasma cells may also be observed in areas of old infarcts in the kidneys, just as in other organs. (Fig. 1.)

Polymorphonuclear leukocytic infiltration, however, remains the safest criterion, even if these cells accumulate in only small clusters.

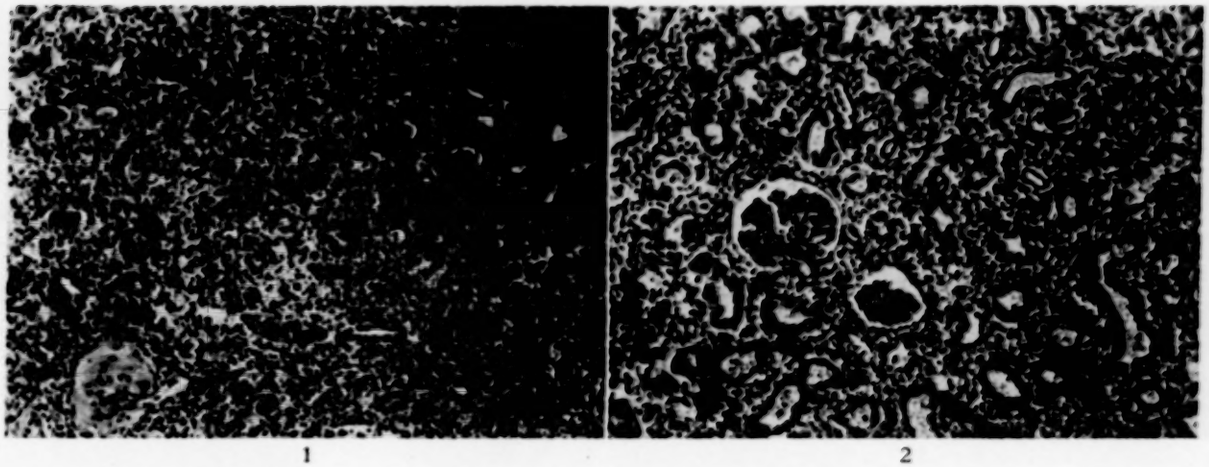

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FIG. 1. Chronic active pyelonephritis. Pleomorphic infiltration with polymorphonuclear leukocytes in tubular lumina. Hematoxylin and eosin stain, original magnification × 120.

FIG. 2. Interstitial nephritis (scarlet fever). Hematoxylin and eosin stain, original magnification × 120.

Pyelonephritis must be distinguished from other forms of interstitial nephritis of basically different pathogenesis. Most of the latter are not infectious, i.e., they do not result directly from microorganisms, and may occur under a variety of circumstances [*24–26*]. In some of them, as in scarlet fever or other infectious diseases, or as a reaction to sulfonamides or other antibiotic agents, there is a strong suggestion that the process is of an allergic nature. A similar pathogenesis has been commonly assumed in Weil's disease, although this is not universally accepted [*26*]. Interstitial nephritis also occurs in many instances of acute tubular nephrosis [*24,25*], and in transplanted kidneys where it is believed to be allergic in nature [*27*]. There is as yet no unanimity of opinion of its pathogenesis and indeed there may be different types.

The distinction of pyelonephritis from interstitial nephritis may often be difficult. (Fig. 2.) The kidney in interstitial nephritis is enlarged and its surface smooth, unless this process is superimposed upon pre-existing chronic disease. The histologic features of interstitial nephritis are those described as a facet of what is now known under the term of tubular nephrosis, in which the interstitial inflammatory infiltrate may be conspicuous or even predominant. Its cellular composition and distribution may resemble closely that of subacute pyelonephritis but there are significant points of differences. The damage to the tubular apparatus most commonly is diffuse in tubular nephrosis, whereas it is patchy in pyelonephritis. In pyelonephritis it consists mainly of focal destruction of segments of tubules by the interstitial infiltrate, or atrophy in later stages. Degenerative changes in tubular epithelial cells in tubular nephrosis, although variable in type and intensity may be, and often are, independent of interstitial infiltration and occur in areas free of inflammation; in pyelonephritis they occur only in conjunction with it. Furthermore, dilatation of cortical tubules with flattening of the epithelial lining is distinctive of tubular nephrosis and does not occur in pyelonephritis except in its end stage when the tubules are filled with homogeneous casts. Abscesses and polymorphonuclear leukocytes in tubular lumina are not seen in tubular nephrosis but are characteristic of pyelonephritis.

The evidence, one way or another, occasionally may not be decisive, particularly since pyelonephritis may in some instances be associated with tubular nephrosis. It is not likely, however, that all interstitial infiltrate in tubular nephrosis is due to complicating pyelonephritis [*28*], for polymorphonuclear leukocytic infiltration is absent or minimal in tubular nephrosis, whereas it should be predominant if this were an early stage of pyelonephritis.

Thyroid-like Areas (*Fig. 3*). This change was first described by Ponfick (quoted [*4*]), and has been recognized as the most reliable criterion of pyelonephritis since the classic study of Weiss and Parker [*6*]. There is no doubt that dilated ducts with flattened epithelial cells, filled with homogeneous colloid material, are frequently seen in the later stages of chronic or healed pyelonephritis. The question remains whether or not this change is pathognomonic.

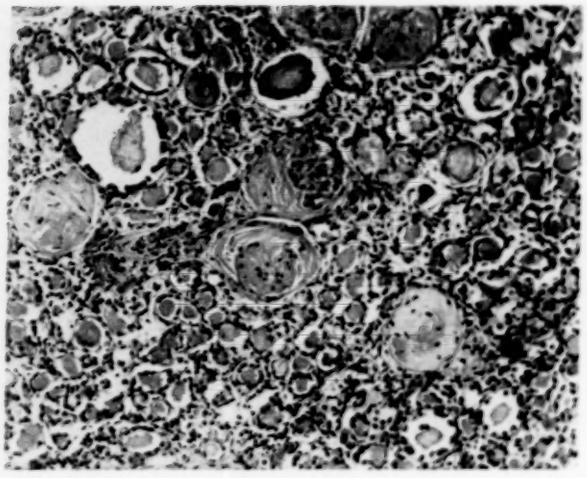

FIG. 3. Chronic pyelonephritis with thyroid-like areas with interspersed hyalinized glomeruli and atrophic tubules. Hematoxylin and eosin stain, original magnification × 120.

The dilatation of tubules is thought to be the result of a pinching off at one or two levels of their course. Fahr [*20*] refers to them as retention cysts, De Navasquez [*29*] as internal hydronephrosis. The colloid material is presumed to be derived from disintegrated polymorphonuclear leukocytes since the basophilic material in earlier phases can be identified as nuclear fragments of polymorphonuclear leukocytic casts [*30*]. We have applied the Feulgen stain for nucleic acids in some of our cases and found that the intensity of the Feulgen stain roughly parallels the basophilic character of the casts, and that most of the eosinophilic ones do not take the stain. It has also been proposed that the hyaline casts derive directly from the acute inflammation, namely, by stuffing of tubules with pus [*31*]. We do not believe that a definitive statement concerning the origin of these casts can be made. The derivation from nuclear material and disintegration of cytoplasm in some of them seems assured, but the possibility cannot be excluded that others derive from tubular excretion of proteinaceous material into the lumina [*4*].

In addition to pyelonephritic scarring, cystic dilatation of tubules and hyaline casts may occur in a significant number of cases without evidence of acute, chronic or healed inflammation. Such thyroid-like areas occur specifically in conjunction with three conditions. One relates to the so-called "barrier zone" which, as we shall demonstrate, is ischemic and not pyelonephritic in origin. Here the dilatation is often only moderate. Secondly, thyroid-like areas are frequently found in conjunction with dysplasia, especially in immediate juxtaposition to or intermingling with groups of cystic spaces lined by high cuboidal epithelium or, for that matter, next to any type of space-occupying lesion. Such areas, small or large, are conspicuous by the absence of any interstitial inflammatory infiltrate or scars. Finally, thyroid-like areas occur in hypoplastic kidneys. A detailed description of the pathognomonic features of this association has been published by Fahr [*20*] under the term of "hypogenic nephritis." For the purposes of this study we refer only to such areas of dysplasia that are not complicated by inflammation.

The thyroid-like areas in hypoplastic kidneys are aglomerular, and the dilated tubules are closely approximated, occasionally revealing the characteristics of primitive ductules [*32,33*]. (Fig. 4). Smooth muscle and cartilage have been described in these areas [*20,32*]. In hypoplasia, medullary malformation is readily distinguished by its fibrillary, moderately cellular connective tissue stroma with basophilic matrix supporting a paucity of atypical, often branching collecting tubules. (Fig. 5.) By contrast, in chronic or healed pyelonephritis patches of cystically dilated tubules are separated by strands of connective tissue, collapsed tubules and scattered hyalinized glomeruli. An inflammatory infiltration may be secondary to the malformation.

It has been postulated by Zollinger [*34*] that the absence of glomeruli is due to their destruction in the course of acute pyelonephritis in early childhood. This may be an adequate explanation in some instances but those cases observed in our series to lack glomeruli showed definite evidence of malformation, namely, hypoplasia of the medulla with moderately cellular embryonic stroma, rather than hyalinization and scarring. These cases may also exhibit intracortical dysplasias.

Thyroid-like areas *per se*, therefore, cannot be regarded as pathognomonic for pyelonephritis.

"Barrier" or "Intermediate" Zone. The German literature frequently refers to a "barrier zone" [*4,19,20*] at the corticomedullary junction as a finding characteristic of chronic pyelonephritis. It is described as a distinctive zone of connective tissue at the cortical aspect of the medulla, containing a few, occasionally dilated tubules with hyaline casts. It is conceived as a sequel to inflammation of the medulla which, in its chronic stage, is characterized by lymphocytic and plasma cell infiltration, and later by the

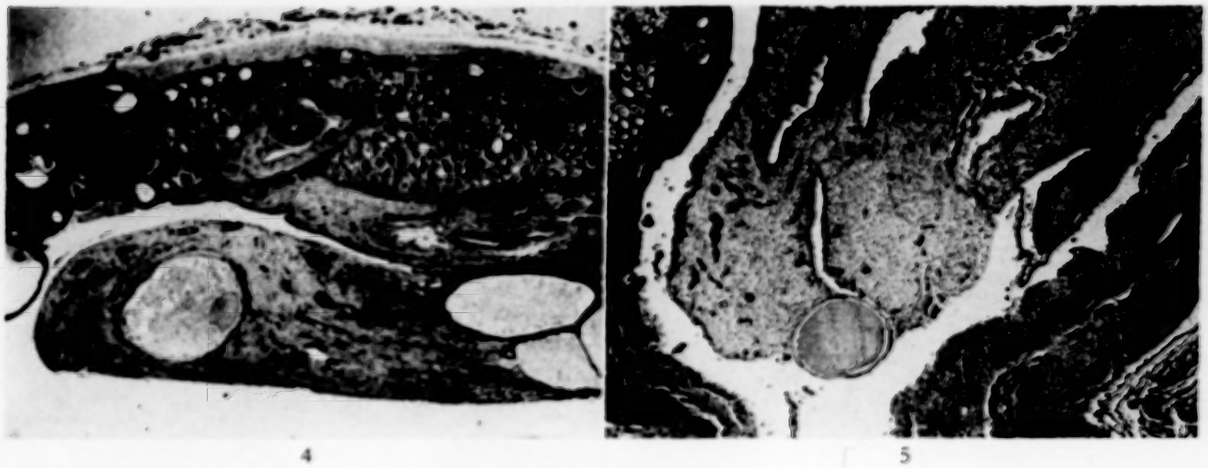

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FIG. 4. Hypoplastic kidney. Cortex shows thyroid-like area, aglomerular. Note the hypoplastic, cystically malformed medulla. Hematoxylin and eosin stain, original magnification × 16.

FIG. 5. Hypoplastic medulla of a patient similar to that of Case 4. Note the relative cellularity of stroma (as distinguished from atrophy with hyalinization). Hematoxylin and eosin stain, original magnification × 34.

appearance of a zone of proliferation of fibroblasts which produce collagen. We have seen this zone many times but our studies lead us to assume that ischemia is the origin of this lesion.

The process involves much or all of the medulla and respective cortex, corresponding to a macroscopically apparent flat cortical scar, with contraction of the medulla and retraction of papilla, thus resulting in a confluence of minor calices into a single dilated major calyx. The barrier or intermediate zone itself can be recognized with the naked eye as a thin, dark red strip between the flattened medulla and the thinned cortex.

The barrier zones which we have identified by the features described in detail by Staemmler and Dopheide [*1*] were always associated with characteristic changes in the cortical tissue immediately adjacent. The latter shows one of two changes. It is either markedly scarred, containing few residual tubules and crowded hyaline glomerular knots, or reveals acute coagulation necrosis in an area of scar formation.

The hyalinized glomeruli in these areas, when stained by the periodic acid-Schiff (PAS) method, differ distinctly from those in pyelonephritic scarring. The outline of the glomerular capillaries can still be made out, although less distinctly than normal, appearing blurred. The glomerular tufts completely fill Bowman's spaces and may blend with the capsular basement membrane, which shows similar changes.

At the corticomedullary junction proper a more or less narrow zone is seen which is much more cellular than the medulla, composed mainly of atrophic tubules and varying degrees of round cell infiltration and some connective tissue. The tubules often contain hyaline casts and are occasionally dilated. In contrast to the overlying necrotic or scarred cortex and the underlying medulla, this intermediate zone contains blood-filled vessels.

The cortical aspect of the medulla, even in its hyalinized stage, shows relatively well preserved basement membranes of the tubules. They are often thickened and stand out clearly with PAS stain. This indicates that they were not destroyed by granulation tissue in this zone if, indeed, granulation tissue ever preceded this change. We are not impressed with the predominance of fibroblastic proliferation at any stage of the development of the intermediate zone. Close analysis reveals that in the areas of dense cellularity only a few nuclei belong to either lymphocytes and plasma cells, and most of them are those of atrophic tubular epithelial cells. Fibroblasts and fibrocytes are rarely noted in large numbers.

The barrier zone, therefore, is an ischemic process involving adjacent medulla and cortex and is invariably related to focal vascular lesions. These consist of partial or complete occlusion of interlobar arteries by hyperplastic arteriosclerosis or organized thrombi. The term barrier zone was given to this zone because it was conceived as a barrier to the urinary downflow by granulation tissue and scar formation. Since,

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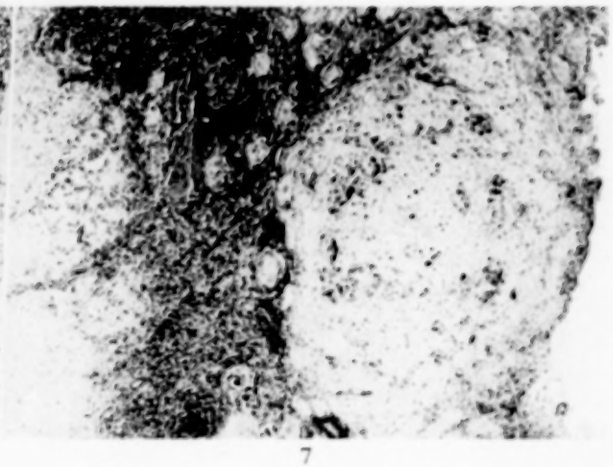

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FIG. 6. Old infarct with relative preservation of intermediate and subcapsular zones. Also note relative preservation of peripheral portion of medulla next to peripelvic fat tissue. Hematoxylin and eosin stain, original magnification × 10.

FIG. 7. Infarct of approximately same stage as in Case 6. Somewhat higher magnification. Note the hyalinization of medulla and cortex with cellular intermediate zone. There is iron pigment in the cortical infarct. Hematoxylin and eosin stain, original magnification × 35.

however,—as we propose—the process is related to ischemia, involving both the cortex and medulla, separated from each other by a zone which has a partially preserved blood supply, we prefer the term intermediate zone.

To substantiate our concept of its pathogenesis, we examined various stages of embolic or thrombotic infarcts in non-pyelonephritic kidneys. We found essentially the same features in recent and old infarcts as in pyelonephritic kidneys with intermediate zones and related cortical and medullary lesions. It is apparent from this study that any obstruction of the interlobular artery (Fig. 6) close to the arcuate artery results either in ischemic infarct or atrophic scar in the cortex. (Fig. 7.) Most of the arterial supply to the medulla through the vasa recta spuriae is thus obliterated, leading either to ischemic infarction or atrophy of most of the medulla, with partial preservation of the tubular basement membranes.

Two phenomena remain to be explained. First, the relative preservation of tissue at the corticomedullary junction proper, which makes the zone of hyalinized medulla so conspicuous. This phenomenon may be understood if we accept the observations of Block [*35*] in experiments with dogs and Moses et al. [*36*] in rabbits. Block concluded from injection preparations that under reduced pressure the corticomedullary junction is better supplied with blood than either the cortex and the medulla. This can also be shown by postmortem injection of human kidneys. In a preliminary study we were able to demonstrate selective filling of arteries at the corticomedullary junction.

The second phenomenon is a partial preservation of tissue at the lateral aspects and the apical portions of the medulla. We believe these areas are better preserved because of an accessory blood supply from the spiral artery [*37*], a situation analogous to the preservation of a narrow subcapsular zone of cortical tissue because of capsular blood vessels.

Tubular Atrophy. Atrophy of tubular epithelium, collapse of lumina, interstitial edema and fibrosis are important features in certain phases of subacute and chronic pyelonephritis, since they account for the loss of function related to the tubular apparatus at a time when glomerular filtration is presumably still within the normal range. Indeed, during this stage most glomeruli appear normal but rather closely crowded and ischemic.

This process closely resembles that of vascular atrophy (incomplete infarction) but its pathogenesis may not be the same in all cases [*29*]. Since portions of the tubules are destroyed by acute inflammation, it is possible that the remaining distal sectors may undergo atrophy due to inactivity. Whether or not chronic interstitial inflammatory infiltration, which rarely invades the tubules, can bring about atrophy by circulatory impairment can only be assumed by inference. The vascular lesions proper, however, are almost invariably demonstrable and may

occur as soon as six months [6], and readily account for tubular atrophy by ischemia.

Vascular Changes. It is of interest to note that the vascular changes are minimized in the older literature. Recent authors emphasize their prominence. Arteriosclerosis, productive endarteritis and other arterial lesions are indeed most commonly associated with chronic pyelonephritis. This becomes all the more striking when these changes are confined to the affected pyelonephritic kidney if the opposite kidney is normal, of if the vascular changes are more conspicuous in limited areas involved by pyelonephritis in one kidney and contrast with the more normal portions, or if the vascular changes occur in young persons with chronic pyelonephritis.

There is no need for discussing these vascular changes in detail. They are clearly described by Weiss and Parker [6] as hyperplastic arteriosclerosis of varying degrees of cellularity, the peak of concentric proliferation of intimal cells being closely related to the degree and type of hypertension. They stress the occurrence of fibrinoid necrosis in malignant hypertension and the infrequency of hyalinization of arterioles. A clear distinction between these vascular lesions and ordinary arteriosclerosis in interlobar and arcuate arteries cannot always be made, since hyperplasia of the intima is one of the major characteristics of arteriosclerosis anywhere and the difference is more quantitative than qualitative. The vascular lesions in pyelonephritis are basically of the same nature as those occurring in senescent renal arteriosclerosis and malignant hypertension, except for their distribution and the relative infrequency of arteriolosclerosis. The causative relationship between pyelonephritis and vascular changes is not easily understood. Inflammatory destruction of arterial walls with thrombosis in acute pyelonephritis and inflammatory endarteritis is described as a common finding at this stage [31]. However, we have observed true inflammatory arteritis only rarely in our material of acute and chronic pyelonephritis and do not regard it as a significant contributory factor in the development of vascular changes in pyelonephritis. In this respect we find ourselves in agreement with Heptinstall [38].

Also, we have paid attention to medial atrophy, as reported by Bell [39]. For, as he concludes, this would indeed mean that the tubular atrophy precedes the vascular changes and that the latter should be interpreted as an "inactivity atrophy." We have, however, been able to find only an occasional artery with fibrosis and hyalinization of the media without significant intimal changes of either the ordinary or the hyperplastic type of arteriosclerosis.

The hypothesis of Weiss and Parker [6] that these vascular changes are attributable to the interstitial inflammation through "edema stasis and products of inflammation" is borne out by the fact that similar vascular changes occur in conjunction with many inflammatory conditions elsewhere in the body. Nevertheless, we believe that the pathogenesis still remains precisely to be elucidated.

Important as is the involvement of arteries in pyelonephritis, we cannot regard this process as pathognomonic. Hyperplastic arteriosclerosis and concentric intimal proliferation cannot be listed as criteria identifying chronic pyelonephritis, for such lesions are non-specific and occur in benign and malignant nephrosclerosis, depending upon the age of the patient and degree of hypertension.

Glomerular Changes. There are several types of glomerular changes in chronic pyelonephritis. None of them, however, are pathognomonic.

Invasive glomerulitis [40]: This type occurs not only in acute pyelonephritis but also in some stages of exacerbation of chronic pyelonephritis. Active interstitial inflammation, predominantly by polymorphonuclear leukocytes, invades the glomeruli from without and may lead to their complete destruction. This accounts for the loss of some glomeruli but, in the total picture, not for many of them.

Degenerative glomerulitis ("alterative" 40): This type of inflammation is secondary to focal necrosis of glomeruli. This process also is not frequent and occurs in cases of pyelonephritis associated with both hypertension and uremia [40]. Fahr [20] was of the opinion that this type of glomerular change in decompensated nephrosclerosis was related to irritation by products of metabolic breakdown in uremia. Others believe that it is the result of excessive work demand due to pronounced reduction of functional parenchyma [41]. The differences in opinion may stem from variations of criteria applied to the glomerular changes under discussion. This becomes evident when one considers that Gross et al. [41] designated the lesion as "proliferative" glomerulitis and found that it occurred in a third of their cases without uremia and hypertension. In our

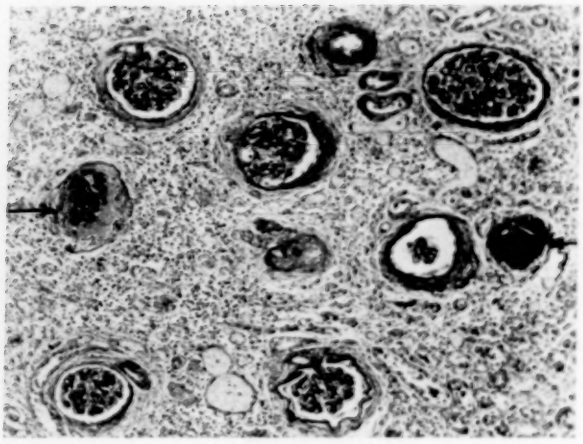

FIG. 8. Capsular fibrosis of glomerulus (Type I) in chronic active pyelonephritis with splitting of basement membrane of Bowman's capsule (periglomerular fibrosis). One glomerulus, indicated by arrow on the left, shows capsular fibrosis (Type II). Another glomerulus, indicated by arrow on the right, is the type seen in old infarctions. Periodic acid-Schiff stain, original magnification × 120.

experience "degenerative" (not proliferative) glomerulitis is rarely seen in azotemia unless associated with hypertension, i.e., presumably vasospasm. Kleeman et al. [*42*] seem to have had a similar experience, and essentially they agree with our interpretation.

Uremic pericarditis: Thinking that the conditions under which uremic pericarditis occurs are comparable to those of degenerative glomerulitis, we reviewed 100 consecutive cases of death in uremia. Our analysis from clinical charts revealed twenty-two instances in which pericarditis was diagnosed by auscultation or at autopsy, or both. Five cases (8.8 per cent) occurred in fifty-seven instances of pyelonephritis, twelve (40 per cent) in thirty cases of glomerulonephritis, and five (38 per cent) in thirteen cases of hypertension. All five patients with pyelonephritis and uremic pericarditis also had hypertension. We do not know the pathogenetic significance but we do notice that in pyelonephritis both degenerative glomerulitis and fibrinous pericarditis occur in uremia only when hypertension is present. In our experience from autopsies, uremic pericarditis is rare without hypertension. The only noteworthy exception occurs in uremia from acute tubular nephrosis.

Capsular fibrosis: This process may occur in two apparently different forms. Both are proliferating, hyalinizing processes originating apparently in Bowman's capsule; both frequently appear in areas of pyelonephritic scarring and atrophy and therefore seem to suggest different phases of the same process, were it not for the fact that transitional stages are difficult to recognize if indeed they exist. We have diligently searched for them in sections revealing large numbers of both forms but only rarely did we find instances which could be interpreted with some stretch of the imagination as an intermediate stage of development.

Capsular Fibrosis Proper (Type I). This is frequently referred to as periglomerular fibrosis, although the proliferation of fibroblastic elements invariably involves the basement membrane of Bowman's capsule (Fig. 8), and is characterized by its thickening, splitting and frequent interruptions. The concentrically arranged ring of fibroblasts is commonly situated on both sides of the altered basement membrane and is lined by intact epithelial cells at the urinary space. This process continues onto dense hyalinization. The glomerular tufts, though atrophic, are usually well preserved and rarely show adhesions to the capsule.

Intracapsular Hyalinizing Fibrosis (Type II). This seems to be totally different from Type I when seen in hematoxylin-eosin preparations, for such glomeruli appear as hyalinized knots with complete obliteration of the urinary space. (Fig. 9.) Their true nature can be revealed best by PAS or Alcian blue-PAS stain or by Luxol fast blue-PAS stain. (Fig. 10.) The hyaline knot can then be seen to consist of a small "obsolescent" glomerular tuft, shrunken toward the pole, and a separate crescent-shaped mass filling all of Bowman's space, adherent both to the glomerular tuft and to the capsule. It is stained rather lightly with PAS and in combination with Alcian blue the thickened, wrinkled basement membrane of the glomerular tuft is sharply contrasted. It often contains much sudanophilic material and many reticulin fibers, demonstrated with silver stain. This intraglomerular mass contains varying numbers of spindle-shaped nuclei, arranged in a more or less concentric pattern. Because of their shape, distribution, and their often considerable number, they cannot be regarded as entrapped epithelial cells. Rather, they resemble collagen-producing mesenchymal elements, possibly deriving from Bowman's capsule to which they are intimately adherent. The basement membrane of the capsule is thickened and often split but is only occasionally interrupted, or finally may disappear completely.

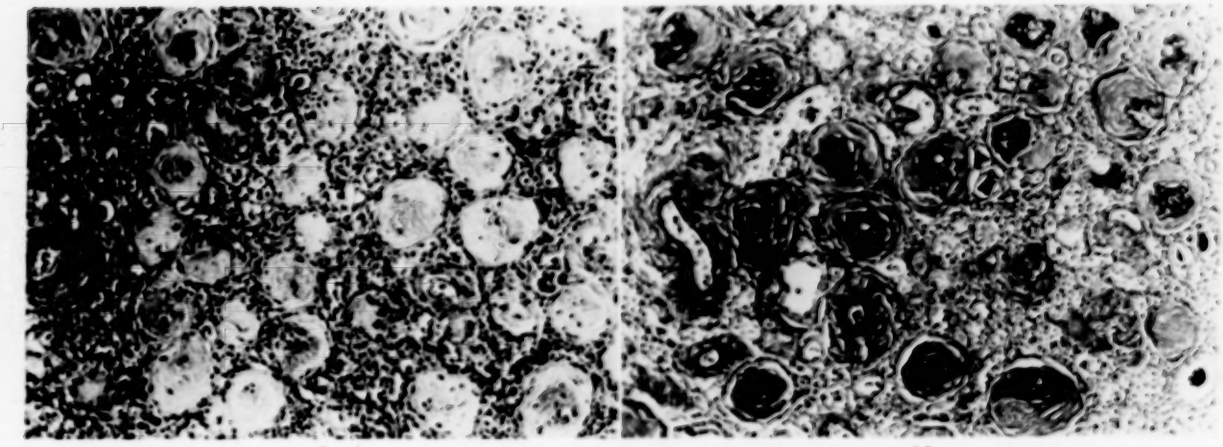

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FIG. 9. Chronic pyelonephritis with intracapsular hyalinizing fibrosis (Type II). Note the somewhat darker central portion corresponds to PAS positive glomerular tufts as seen in Case 10. Hematoxylin and eosin stain, original magnification × 120.

FIG. 10. Same as Case 9. Periodic acid-Schiff stain, original magnification × 120.

In fact, the integrity of the basement membrane in most of these glomeruli is a conspicuous feature. Even though fibroblastic proliferation of Bowman's capsule is noted, we could only rarely observe on serial sections a focus which might possibly be interpreted as "invasion" from the outside into the capsular space.

We have not been able to establish a satisfactory concept of the histogenesis of either form of fibrosis. Both occur commonly in areas acceptable by our standards as the sites of pyelonephritic scarring with evidence of ischemic atrophy.

Capsular fibrosis proper has been regarded in the past as an inflammatory proliferation, an interpretation suggested by its frequent occurrence in chronic pyelonephritis. This thesis is indeed attractive, for this form of capsular scarring not only is common in chronic pyelonephritis but can be seen without significant vascular changes, particularly in experiments with animals [*43*]. These cases of chronic pyelonephritis in rats with well developed capsular fibrosis are conspicuous by their lack of vascular involvement. It should not be overlooked however, that this type of capsular fibrosis can also be found in areas of ischemic atrophy, without any evidence of preceding inflammation. We have seen it in cases of renal atrophy due to partial thrombotic occlusion of the main renal artery.

Intracapsular hyalinizing fibrosis—much more common than capsular fibrosis in chronic pyelonephritis—is definitely related to ischemia and not to the pyelonephritic process proper. It is a frequent finding in simple arterio- and arteriolosclerosis. To our knowledge, the lesion was first sketched and beautifully illustrated by Mcmanus [*41*] who registered it as "arteriosclerotic obsolescence." We have not been able to find an adequate explanation of this peculiar change, for in addition to simple atrophy there is cellular proliferation and deposition of a hyaline material which obliterates Bowman's space, and contains mucopolysaccharides, fat and reticulin. This mass is found outside the glomerular tufts and derivation from the Bowman's capsule is strongly suggested.

Finally, there is the problem of the ultimate fate of hyalinized glomeruli in chronic pyelonephritis. We presume that some of them may be absorbed by invading granulation tissue, for such observations, though isolated, have been reported (Putschar [*19*] and others). For the most part, however, it seems to us that they remain indefinitely as hyalinized knots.

We have not been able to observe any features distinctive of hyalinization of glomeruli in pyelonephritis, as contrasted to nephrosclerosis. We agree with Staemmler and Dopheide [*4*] that the fibrous knots rarely remain in an open capsular space, as McManus suggested [*44*].

Summary of Diagnostic Criteria of Chronic Pyelonephritis. The macroscopically observed *flat scar* is as often due to ischemia as to chronic pyelonephritis. An active pleomorphic *inflammatory infiltrate*, and particularly accumulation of polymorphonuclear leukocytes, remains the safest

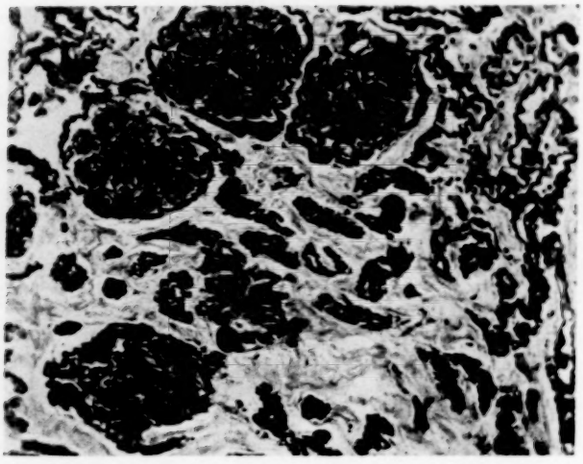

FIG. 11. Glomeruli in old infarct. High power magnification from old infarct illustrated in Figures 6 and 7. Periodic acid-Schiff stain, original magnification × 240.

criterion for the diagnosis of chronic pyelonephritis. In the absence of active inflammation, i.e., in the healed stage, the diagnosis of pyelonephritis can be made by inference, but only if for each of the criteria mentioned causes other than pyelonephritis are eliminated.

The most suggestive criterion is areas of *thyroid-like* appearance. These can be taken as evidence of sequelae of pyelonephritis if they are not found in the vicinity of expanding lesions such as cysts or tumors, if they are not part of an intermediate zone, and if they are not of congenital origin.

Glomerular changes are of relatively limited value in distinguishing pyelonephritic from ischemic scars. It may be stated in general that hyalinized glomeruli in chronic pyelonephritis are placed irregularly, separated by atrophic or dilated tubules (Fig. 11), while the hyaline knots in more or less complete infarcts are closely and solidly packed. Glomeruli in scars of infarcts are readily distinguishable from other types of glomerular fibrosis.

The *intermediate zone* and *tubular atrophy* are ischemic phenomena and related to chronic pyelonephritis only insofar as they are sequelae of arteriosclerotic lesions which happen to occur in the wake of pyelonephritis.

Chronic *pyelitis* may be present when intrarenal inflammation has subsided. In such instances it may not be possible to determine whether or not the process is a residue of a healed chronic pyelonephritis.

Finally, we should realize that it is not always possible to establish a definitive pathogenesis in the late stages of scar formation and that an interpretation should be designated conjectural unless a supporting clinical history is available.

TABLE I
PREVALENCE OF CHRONIC PYELONEPHRITIS

Total No. Postmortem Examinations	Chronic Pyelonephritis		
	No. (%)	Diffuse No. (%)	Focal No (%)
3,393	97 (2.8)	15 (0.4)	82 (2.4)

STATISTICAL SURVEY

We applied the aforementioned rather rigid criteria to a review of our cases and attempted to distinguish "focal" from "diffuse" chronic pyelonephritis. This distinction was made because focal pyelonephritis obviously may be of no significance in respect to total renal function, except for its conceivable effect on the blood pressure. To some extent this separation is arbitrary, for multiple focal scars may involve a considerable portion of the kidney, although not all of the renal parenchyma, and reduction of kidney weight is reliable only in the extreme instance. It may be influenced by complicating conditions, such as concomitant severe nephrosclerosis and nephrolithiasis or hydronephrosis, if weighed before opening the pelvis. A kidney weight of less than 110 gm. was considered to be significant.

Of a total of 3,393 patients at autopsy, chronic pyelonephritis was identified in 97 or 2.8 per cent. Of these, 15 or 0.4 per cent were classified as diffuse and 82 or 2.4 per cent as focal pyelonephritis. (Table I.) It may be of interest to note that almost 50 per cent of the patients listed as having pyelonephritic scarring in our files were considered not to meet the rigid standards which evolved during this study. Were these patients to be included, the ratio would rise to 5.8 per cent incidence of chronic pyelonephritis, a figure comparable to that of several previous statistics. (Table II.)

An attempt was made to determine how many of these ninety-seven cases of chronic pyelonephritis were of clinical significance. Blood pressure values for the most part were incon-

TABLE II
REVIEW OF LITERATURE ON INCIDENCE OF CHRONIC PYELONEPHRITIS

Authors	Year	% Incidence	Remarks
Bugbee and Wollstein [8]	1924	4.5	Children
Gibson (quoted from [9])	1928	6.0	...
Pfeiffer (quoted from [19])	1932	1.9	...
Butler et al. [9]	1937	2.0	Children
Jackson et al. [10]	1955	9.0	...
Brod [7]	1956	6.2	...
Zollinger [13]	1957	7.0	...
MacDonald et al. [11]	1957	15–20	...
Raumanis et al. [12]	1959	20.0	Chronic disease hospital
Kleeman et al. [42]	1960	15.0	...

clusive because a large number of patients were admitted terminally with hypotension. An increased heart weight was not considered to be absolutely indicative of hypertension. Serum non-protein nitrogen determinations, however, were available in almost all cases. A value of more than 70 mg. per cent was accepted as indicative of azotemia, although a single instance of 45 mg. per cent in a child five years of age with neurogenic bladder and bilateral renal contraction was also accepted as failure of renal function. In three cases of chronic bilateral pyelonephritis no non-protein nitrogen determinations were available.

Of the total of ninety-seven patients (Table III), we found eighteen with azotemia, an astonishingly small proportion, amounting to no more than 18.6 per cent (or 0.54 per cent of the total autopsy material). Only four of the patients with unilateral pyelonephritis showed azotemia, and all of them were found to have acute pyelonephritis in the opposite kidney.

Of the eighteen patients with chronic pyelonephritis with azotemia, thirteen or 72.2 per cent were complicated by either hydronephrosis (nine), dysplasia (two) or calcinosis (two). Of these same patients, in thirteen pyelonephritis was due to obstruction of the lower urinary tract, and in five it was of the non-obstructive type. Of the thirteen with obstructive chronic pyelonephritides, in nine it was bilateral, and in four it was unilateral; but, in all four patients it was complicated by contralateral acute pyelonephritis.

TABLE III
INCIDENCE OF PYELONEPHRITIS WITH AZOTEMIA

Total no. of cases at autopsy	3,393
Total no. of cases of chronic pyelonephritis	97
Cases with azotemia	18
Obstructive	13
Bilateral	9
Unilateral	4
Non-obstructive	5

A tabulation of age groups and sex (Table IV) shows the proportion of male to female to be 1 to 1.3, in contrast to predominance of males which has previously been noted in autopsy statistics [19]. It also reveals the highest prevalence between the ages of sixty and eighty years. These figures, however, are misleading (as they are in other statistics) since the comparative prevalence for age groups and sex must be calculated on the number of autopsies for each age group and each sex separately. We have therefore calculated the percentage of cases of chronic pyelonephritis not only in relation to the total of 3,393 autopsies but also in relation to the number of cases per decade.

Because of the relatively high average age of death at the Milwaukee County Hospital (61.8 years), the largest number of cases are observed in the age groups from sixty to eighty years, but the breakdown into decades does not show a statistically significant difference in prevalence of any age group from twenty-one to 100 years. Since only one patient was observed in the age groups from birth to twenty years of age, no conclusions were drawn.

Noticeable is the relatively small number of clinically significant cases of pyelonephritis, i.e., in which death can be attributed to azotemia (0.54 per cent). This obviously is related to the small number of patients with bilateral diffuse chronic nephritis (0.4 per cent), not all of whom showed azotemia. This finding is in sharp contrast to the statistics of pyelonephritis in childhood and infancy, in which uremia is said to be the most common cause of death [9]. Our statistics do not include the peak in childhood but the fact remains that in all other age groups, death in patients with chronic pyelonephritis could be attributed to the renal disease in less than 20 per cent.

Our statistics show a relatively low prevalence of chronic pyelonephritis, particularly in comparison with the most recent statistics. (Table II.) It is, of course, possible that lesser degrees of

TABLE IV*

RELATION OF CHRONIC PYELONEPHRITIS TO AGE AND SEX

Age (yr.)	Pyelonephritis		Correction per Decade		Correction per Sex			
					Male		Female	
	No. Cases	% of 3,393	No. Autopsy Cases	% of Pyelonephritis	No. Cases	% of 2,107	No. Cases	% of 1,286
0–1	0	0	264	0	0	0	0	0
1–10	1	0.03	101	0.99	1	0.05	0	0
11–20	0	0	67	0	0	0	0	0
21–30	4	0.11	106	3.78	4	0.19	0	0
31–40	4	0.11	130	3.09	2	0.09	2	0.16
41–50	6	0.17	337	1.78	4	0.19	2	0.16
51–60	13	0.38	437	2.97	6	0.28	7	0.54
61–70	25	0.73	706	3.54	16	0.76	9	0.69
71–80	26	0.76	812	3.20	14	0.66	12	0.93
81–90	17	0.50	399	4.26	7	0.33	10	0.78
91–100	1	0.03	34	3.30	1	0.05	0	0
Total	97	2.82	3,393	...	55	2.59	42	3.26

* Male:female = 1:1.3.

focal pyelonephritis may have remained unlisted. A retrospective review of material at autopsy with only a limited number of tissue blocks available cannot rule out the occurrence of small, grossly unnoticed foci of pyelonephritis. Conversely, we have eliminated about half of the cases previously classified as chronic pyelonephritis since they no longer meet the criteria herein outlined. It seems to us, therefore, that the standards set for identification have much to do with the reported prevalence of chronic pyelonephritis in any study.

Childhood pyelonephritis is excluded from our survey by circumstances, but it is apparent that chronic pyelonephritis in the older age groups is less meaningful in respect to renal function than might be expected. Its relation to hypertension will be discussed separately.

PREDISPOSING FACTORS

Irrespective of the pathway by which the bacteria arrive in the kidney, certain predisposing factors are known which favor the lodgement of microorganisms, with subsequent pyelonephritis. They have been enumerated in detail by various authors [*19,42,45–47*] and can be grouped in the following categories: (1) Pathogenicity of organisms; (2) obstruction (intra- and extrarenal, functional or mechanical); (3) congenital abnormalities of urinary tract; (4) iatrogenic factors; (5) metabolic diseases (diabetes, etc.); and (6) pregnancy.

Pathogenicity of Organisms. It is strange that normal inhabitants of the intestinal tract, i.e., E. coli and Aerobacter aerogenes are commonly found in acute pyelonephritis, whereas the microorganisms which so frequently are the cause of acute purulent infection elsewhere, i.e., gram-positive cocci, are commonly found in chronic pyelonephritis [*3,46*]. Just what the particular circumstances are which determine their pathogenicity and their effect on the kidney is not known. The presence of urine is itself likely to play a role since the rate of bacterial growth in urine is rapid as compared to other media [*48*], and urinary stagnation is an important factor in the genesis of pyelonephritis. Changes in the content of urea, sodium, potassium, glucose and proteins do not seem to play a significant role [*46*].

It is apparent, however, that the presence of urine, its pH, and the concentration of substances excreted in it are not the only factors. There is ample evidence of differences in the resistance of various species to the same type of organism, in individual host susceptibility, and in variability of the virulence of one and the same strain of microorganisms [*43,49*]. We should indeed endeavor to learn more about the local reaction of renal tissues to the invading organism, for it has become apparent that only 10 per cent of patients with pyelonephritis can be treated successfully, despite the availability of potent antibiotics [*48*].

Obstruction of Urinary Outflow. This factor is obviously the most important, although not the only one since hydronephrosis, if unilateral, may occur without infection even when there is marked contraction of the parenchyma. The obstruction may be congenital or acquired, and may be situated anywhere in the urinary tract from the urethra on up to the calices or even intrarenal units of nephrons. The obstruction may be mechanical, by stones, scars and tumors, etc., or it may be entirely functional, as in disturbances of bladder innervation, lack of ureteral peristalsis, and vesical-ureteral reflux with or without reversal of peristalsis [*50*].

All this has been demonstrated time and again by clinical experience, which Beeson [*45*] summarizes by stating that pyelonephritis occurs twenty times as often in children with anomalies of the urinary tract as without, and twelve times as frequently with obstruction as without. The significance of obstruction of urinary flow in conjunction with bacteremia has also been shown by various animal experiments, notably those of Mallory et al. [*30*], and others [*49,51,52*]. Intrarenal obstruction has been produced by scar formation by focal Staphylococcus infection [*29*] and by microcauterization of medullary portions [*53*]. Pyelonephritis superimposed on potassium deficiency also is probably due to intrarenal urinary stasis, secondary to hyperplasia of epithelium in the tubuli recti [*54–56*]. Pyelonephritis secondary to experimental renal hypertension produced by unilateral nephrectomy with the administration of desoxycorticosteroid likewise falls into this same category, since it is associated with tubular dilatation indicating urinary stagnation [*57*].

Congenital Abnormalities. A number of reports from pediatric clinics attest to the fact that pyelonephritis is more common in infants and children with urinary tract malformation than without [*8,9,14,16,45,58,59*]. These reports, however, do not always distinguish obstructive lesions from other types of malformations, and in the list of pyelonephritides are included unilateral absence of kidneys, cysts, etc., i.e., lesions for which a direct causative relation to pyelonephritis is not clearly established. Apart from such abnormalities which result in impairment of urinary flow, it is quite apparent that hypoplasia or dysplasia may render the kidney more susceptible to pyelonephritis, as documented in Fahr's [*20*] "hypoplastic nephritis," a type of abnormality included in Weiss and Parker's group [*6*] of renal rickets. Obviously not all of these cases, and not all portions of such kidneys, are involved in pyelonephritis, for it would otherwise be impossible to recognize the underlying abnormality. In fact, this difficulty has been emphasized by Ericsson and Ivemark [*32,33*]. The relationship of hypoplasia to pyelonephritis is similar to that of focal dysplasia, and here again not all dysplasias are associated with pyelonephritis. The criteria for more isolated foci of dysplasia have been defined [*32,33*]. Although we have at times observed ductules and primitive ducts such as have been considered characteristic of dysplasia, they were rare in our autopsy material which, however, is for the most part from older patients. Marshall has stressed the frequency of dysplastic scars in the renal cortex of adults [*60*]. We agree with the frequency of cortical scars but were unable, in the majority of instances, to render a reliable opinion on their pathogenesis. It is, however, quite conceivable that such foci of dysplasia predispose to focal pyelonephritis, for it is not uncommon to find them associated with dilated tubules and colloid casts indicating urinary stasis.

Iatrogenic Factors. There is considerable and indeed heated controversy about the precipitation of cystitis, ureteritis and pyelitis by urinary instrumentation [*45,46,48,61*], but everyone who has performed autopsies on patients who have had indwelling catheters is convinced that a direct relationship exists. Without knowing the clinical history, it can often safely be assumed that an indwelling catheter was used, from the finding of a hemorrhagic and often ulcerative type of cystitis. It is, moreover, futile to reject a causative relation between catheterization and urinary infection in the face of commonly observed "catheter fever." It is well known that bacterial endocarditis may be precipitated by urethral instrumentation. Yet, despite the attempts to establish a clear picture of specific conditions and frequency with which focal infection and bacteremia follow instrumentation of the urinary tract, indisputable data are not available [*62,63*].

That catheterization may contribute significantly to true bacteriuria is based mainly on statistical evidence [*64*], and on direct cultures of bladder urine tapped during laparotomy following catheterization. Under these conditions Guze and Beeson [*65*] found microorganisms in the bladder in patients in whom the original non-catheterized urine was sterile. Indirect evidence was produced by Kirby et al. [*66*] who analyzed the cases in which antibiotic-resistant

coliform bacilli were isolated in the urine and found that most of these patients had had previous instrumentation of the urinary tract. They assumed that the resistant microorganisms were acquired in the hospital.

Metabolic Diseases. It has long been known that pyelonephritis occurs more often, perhaps as much as five times more often, in diabetic than in non-diabetic patients [*45*]. Just why the kidney is so much more susceptible in diabetes is not clearly understood, beyond that infections of other organs are equally more frequent in diabetic patients than in non-diabetics. No structural renal change common in diabetes accounts for this phenomenon. Glucose added to the urine does not enhance bacterial growth [*46*].

The relation of other metabolic anomalies to pyelonephritis is also poorly understood except that in potassium deficiency obstructive phenomena are observed in animal experiments. The relationships, however, between salt-losing nephrosis, phosphate retention, tubular acidosis, hypocalcemia, etc. [*67–69*] and pyelonephritis are not clarified.

Pregnancy. Pregnancy is often mentioned as a condition precipitating pyelonephritis. Here again the mechanism of pathogenesis is speculative, for ureteral dilatation is exceedingly common in pregnancy but pyelonephritis occurs only in about 2 per cent of pregnancies [*45*]. A relationship to progesterone could not be established [*70*]. Pyelonephritis usually begins in the second half of pregnancy and seems to have a tendency to be progressive and possibly inducive to toxemia.

Correlation with Clinical Signs and Symptoms. Pyuria: The appearance in the urine of polymorphonuclear leukocytes from the kidney parenchyma depends on the invasion of purulent interstitial infiltrate into the tubular lumina and may therefore be absent in the later stages of pyelonephritis. Leukocytes in the urine may, of course, also derive from the pelvic mucosa but rarely is pyonephrosis found without pyelonephritis. Pyuria does not, of course, always indicate the presence of pyelonephritis; cystitis and ureteritis alone may produce pyuria, which must therefore be evaluated in the light of other findings.

Supravital stains may be helpful. According to studies originating with Sternheimer and Malbin [*71*], supravitally stained leukocytes showing pale staining and Brownian movement of intracytoplasmic particles may be regarded as significant for the diagnosis of pyelonephritis. Poirier [*22*] pointed out that the Brownian movement is apparently dependent upon the osmolarity of the urine, and that the pale staining effect alone is of much greater assistance in establishment of the diagnosis of pyelonephritis. Poirier's analysis of the pale cells under controlled conditions and in relation to renal biopsies seems to have shown that their occurrence, even without Brownian movement, under certain circumstances is diagnostic for early or subacute pyelonephritis. One must not, of course, lose sight of the fact that these cells may derive from blood or from the lower urinary tract. In Poirier's and also in Linneweh's [*68*] series pale cells were found in all cases of active pyelonephritis, provided that more than one specimen was examined. Only 60 per cent of single specimens were positive. Final evaluation of this phenomenon requires further investigation.

Bacterial Count. The most significant progress in the identification of urinary infection was made by quantitative analysis of bacteriuria [*61,64,72,73*]. It is now generally accepted that a count of more than 100,000 bacteria per cu. mm. is indicative of true bacteriuria and rules out contamination. In that sense, true bacteriuria is significant. What it actually means in terms of the patient's disease, that is, whether it reflects a transitory incidental phenomenon, or indicates the presence of cystitis, ureteritis or pyelonephritis, remains to be evaluated.

Not all patients with definite bacteriuria have pyelonephritis. Kass [*64*] found that 10 per cent of the patients in an outpatient department (6 per cent female, 4 per cent male) had asymptomatic infection of the urinary tract, and Grieble et al. [*72*] found unsuspected pyelonephritis in 10 per cent of hypertensive patients, basing his conclusions on quantitative urine cultures in conjunction with the finding of pale cells in the urine. Yet autopsy statistics, although varying widely, reveal an average incidence of 5 per cent, only one-third to one-half of the infections being considered of clinical significance. A more accurate impression of the frequency of pyelonephritis in patients with demonstrated bacteriuria can be obtained from a direct bacteriologic-autopsy correlation, and in such a study of 100 cases of bacteriuria MacDonald et al. [*11*] found active pyelonephritis in 35 per cent. How to interpret the significance of true bacteriuria is therefore not yet certain.

Many attempts have been made to correlate true bacteriuria with pyuria [*61,68,73*], with the appearance of supravitally stained pale cells [*68,72*], with renal biposies [*3,68*], and with other clinical findings. As one might expect, a count of more than 100,000 microorganisms per cu. mm. is not always obtained in cases of known pyelonephritis, and may be present without symptoms or signs of pyelonephritis. Yet a persistent bacteriuria of such propositions warrants the suspicion of infection of some portion of the urinary tract. Correlative and follow-up work in this direction is still needed.

Renal Function. Inasmuch as pyelonephritis affects the tubular apparatus long before the glomeruli and the blood vessels, it is to be expected that tests of renal function show a dissociation of tubular and glomerular function, and that there is an earlier and more profound decline of tubular function than glomerular filtration. Most authors have come to the conclusion that renal plasma flow and tubular function (Tm_D) are proportionately decreased, but that the glomerular filtration rate is relatively well maintained until the later stages of advanced contraction [*7,74–76*]. Kipnis et al. [*21*], however, observed selective tubular dysfunction in only one of thirteen cases. Linneweh [*69*] goes so far as to take the diminished tubular function, as measured by the phenol red excretion test, as an indication of inflammation of interstitial tissue. He finds the reduction of excretion of phenol red more marked in diffuse than in focal interstitial nephritis (pyelonephritis), and has observed improvement in phenol red excretion following treatment of the disease. However, restitution of this tubular function to normal takes longer than the disappearance of pus and bacteria from urine.

When we attempt to interpret the results of specific renal function tests in terms of structural changes we are faced with so many variables that definitive conclusions should be deferred until better correlation with degrees of severity, distribution of lesions and phases of the disease is accomplished.

Needle Biopsy. Because of the focal nature of pyelonephritis, a needle biopsy, even if adequate, cannot reliably reflect the state of renal involvement in pyelonephritis [*77*]. We compared postmortem needle biopsy specimens with six blocks of tissue from the same organ after dissection of the kidney. Of seven patients with active chronic pyelonephritis with adequate biopsy specimens obtained, the diagnosis could be made in four, while in three the biopsy gave no evidence of pyelonephritis. In chronic pyelonephritis, therefore, the needle biopsy is of only limited value in establishing the diagnosis. Yet, even though the finding of normal tissue does not rule out pyelonephritis, histologic changes pathognomonic for pyelonephritis may be helpful in the evaluation of an otherwise equivocal symptomatology.

If combined with bacteriologic studies, a large experience with needle biopsies may eventually shed light on the natural history of pyelonephritis. The interpretation of needle biopsies, however, must be approached with caution. In our series of needle biopsies at postmortem we encountered instances in which colloid casts, capsular fibrosis or tubular atrophy suggested pyelonephritis but in which examination of the kidney later by routine methods identified these lesions as purely ischemic in origin.

Hypertension and Chronic Pyelonephritis. It is the prevailing consensus [*78,79*] that chronic pyelonephritis, even if unilateral, can be considered a cause of hypertension.

Hypertension is said to occur more frequently in cases of chronic pyelonephritis than in control cases. In patients under the age of fifty Braasch [*80*] found hypertension twice as often in pyelonephritis as in control subjects. Brod [*7*] observed hypertension in 59.7 per cent compared to 15 per cent of control subjects. Even over the age of fifty he found hypertension to be associated with pyelonephritis in 84.85 per cent as compared to 30 per cent in control cases. Weiss and Parker [*6*] found hypertension in 60 per cent of their patients with chronic pyelonephritis, and 15 to 20 per cent were of the malignant type.

The frequency with which pyelonephritis is found at autopsy in cases of hypertension depends to a large extent on the criteria used and the extent of involvement considered to be significant. Saphir et al. [*81,82*], for example, has taken an extreme point of view and all but identified malignant nephrosclerosis with chronic pyelonephritis. We attempted to repeat Saphir's study on our material, selecting and analyzing our cases in accordance with his criteria. Of 100 patients with blood pressure of more than 150/90 mm. Hg (average 224/131 mm. Hg) and serum non-protein nitrogen over 55 mg. per cent (most exceeded 100 mg. per cent) we found only fifteen in whom chronic pyelo-

TABLE V

MALIGNANT NEPHROSCLEROSIS AND CHRONIC PYELONEPHRITIS

Data	No.	Average Serum Non-Protein Nitrogen (mg. %)	Average Heart Weight (gm.)	Average Kidney Weight (gm.)	Average Blood Pressure (mm. Hg)	Average Age	Sex	
							Male	Female
Focal subacute pyelonephritis	6	195	680	116	225/130	50.8	5	1
Focal chronic pyelonephritis	4	235	552	138	229/139	56.5	4	0
Diffuse subacute pyelonephritis	1	115	400	160	190/110	59.0	1	0
Diffuse chronic pyelonephritis	4	147	561	100	211/131	51.0	1	3
Total	15	173	548	128	211/127	54.0	11	4

nephritis could be convincingly demonstrated. The pertinent findings are listed in Table v; it may be added that the averages of the blood pressure readings, cardiac weight, kidney weight, non-protein nitrogen values and ages does not vary significantly in these fifteen cases from the remaining eighty-five cases of malignant nephrosclerosis without pyelonephritis. In the majority of instances in this series the malignant nephrosclerosis seems to have been superimposed on pre-existing benign nephrosclerosis.

The question still remains: what is the relationship of chronic pyelonephritis to the vascular changes associated with it and to hypertension? Malignant hypertension occurs in only approximately 15 to 20 per cent of cases of chronic pyelonephritis [*6*] and, in our series of malignant nephrosclerosis, chronic pyelonephritis was found in only fifteen per cent.

The best indirect evidence of a causative relationship lies in the frequency of simultaneous occurrence of both hypertension and chronic pyelonephritis in childhood and young adulthood [*9,69*]. The concurrence cannot easily be waved aside as coincidence.

The sustained fall of blood pressure following removal of the affected kidney in unilateral pyelonephritis would constitute direct evidence that chronic pyelonephritis may be the cause of hypertension. There is no doubt that this has actually been demonstrated, yet it is difficult to determine how often it has been achieved. A review of case reports by different authors [*41,83,84*] leave conflicting impressions. They range from "an occasional return to normal blood pressure" to a significant decrease in hypertension in about half of the patients subjected to unilateral nephrectomy.

The variations in such statistical surveys are due to several factors. In the first place, an unknown and probably large number of unsuccessful cases are not recorded; the successful nephrectomies, therefore, represent at best the maximum achievement. Secondly, an unsuccessful nephrectomy may simply be due to undetected involvement of the opposite kidney. Thirdly, it is not always clear from the case records that the unilateral renal disease actually was chronic pyelonephritis or whether the contraction of the kidney was due to primary vascular disease. The relatively high percentage of cures of renal hypertension in cases selected on the basis of aortography [*85–87*] merely indicates that vascular occlusion and consequent renal contraction may have been the cause of hypertension. In fact, these kidneys may show normal intravenous pyelograms and higher osmolarity, higher potassium concentrations and lower urinary volume than normal. This strongly militates against pyelonephritis as the cause of the arterial disease, for reasons already discussed. In fact, this dissociation is frequently helpful in the clinical differential diagnosis between primary vascular renal disease, glomerulonephritis and chronic pyelonephritis.

Perhaps, something may be learned about unilateral chronic pyelonephritis and its relation to hypertension at autopsy examination. In our series only six such examinations could be made. One patient showed diffuse involvement, five had extensive focal lesions. All were associated with marked vascular changes confined to the affected kidney, without significant arteriosclerosis on the opposite side. The relatively high weight of the kidney in some of these cases of extensive chronic pyelonephritides is attributable to complicating hydronephroses and acute exacerbations of pyelonephritis. (Table VI.) It is likely that not more than two of the six patients (Cases 2 and 5), both with heart weight

TABLE VI
UNILATERAL PYELONEPHRITIS

Data	No.	Kidney Weight (gm.)		Blood Pressure (mm. Hg)	Serum Non-Protein Nitrogen (mg. %)	Heart Weight (gm.)	Age (yr.)
		Left	Right				
Diffuse (left)	1	...	180	130/70	?	290	65
Severe focal (left)	2	115	250	...	...	570	76
Severe focal (left)	3	110	230	130/70	...	250	74
Severe focal (left)	4	...	170	...	25	250	65
Severe focal	5	135	135	...	...	400	88
Severe focal	6	110	190	140/90	33	310	59

over 310 gm., may have had hypertension of significant degree for a significant length of time. Four of the six patients at autopsy with unilateral active chronic pyelonephritis had normal heart weights and showed no other evidence of hypertension.

The occurrence of hyperplastic arteriosclerosis with chronic pyelonephritis does not necessarily mean that the former is a consequence of the latter. We must consider the possibility that the vascular lesion may render the kidneys more susceptible to infection [*43*]. Experiments with animals seem to support this hypothesis [*57*].

Hypertension has not as yet been produced in experimental unilateral pyelonephritis unless the opposite kidney has been removed [*88*]. These negative findings, however, may for various reasons not be applicable to human beings.

Does chronic pyelonephritis produce hypertension in man? Bell [*39*] has concluded from his own experience that hypertension seldom occurs in uncomplicated chronic pyelonephritis and that severe hypertension is usually due to complicating lesions such as nephrosclerosis and glomerulonephritis. From the accumulated direct and indirect evidence we must conclude that pyelonephritic contraction may be the cause of hypertension; the frequency and pathogenesis of this complicated process, however, is still unsettled.

CONCLUSIONS AND COMMENTS

The reliability of morphologic criteria for the identification of chronic pyelonephritis and its sequelae is more limited than generally conceded. We have attempted to outline criteria which can be employed more reliably for this purpose, and find that, using such more rigid criteria, the prevalence of chronic pyelonephritis does not vary significantly from decade to decade, with the possible exception of childhood. It also appears that the clinical significance of this disorder in respect to renal function is less than most recent statistics seem to indicate.

Caution must be exercised in distinguishing the sequelae of primary vascular lesions and developmental abnormalities from changes due to pyelonephritis. Certain guides to that end are offered.

The reliability of estimates of the frequency with which unilateral chronic pyelonephritis causes hypertension is open to question.

The significance of bacteriuria and its relation to pyelonephritis is yet to be evaluated more completely. Bacteriuria cannot at present be identified with "inapparent" pyelonephritis.

We have yet to learn why in a limited number of patients with acute pyelonephritis the disease progress into a chronic non-obstructive phase, and whether indeed this insiduous process is a continuation of pyelonephritis, as originally defined, or whether it is of an altogether different nature.

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Clinicopathologic Conference

Cholecystectomy Followed by Ascites, Jaundice, Splenomegaly and Coma

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D., of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

A TWENTY-THREE year old white woman (N. K.), was transferred to the Barnes Hospital on January 7, 1959, in a comatose condition. The history was obtained from her husband and the referring physician.

The patient had been frail but presumably in good health until November 1958 when vague discomfort developed in the right upper quadrant of her abdomen. Her physician arranged for a cholecystogram. He said that her gallbladder did not visualize, and advised a cholecystectomy. A normal, thin-walled gallbladder, free of stones, was removed; no description of the liver or other abdominal organs was made. Shortly after the patient returned home, her abdomen began to swell. The accumulation of ascitic fluid was moderately well controlled by injections of a diuretic preparation containing both theophylline and an organic mercurial compound. Several weeks later she complained of anorexia, became jaundiced, and was readmitted to the hospital.

Laboratory studies at that time included a positive reaction to the cephalin cholesterol flocculation test, serum albumin 3 gm. per 100 ml., serum globulin 1.7 gm. per cent, serum bilirubin 4.5 mg. per cent, and serum glutamic oxaloacetic transaminase (SGOT) 320 units. The patient was regarded as having viral hepatitis and was treated with an unknown amount of adrenocortical steroids. Muscle hyperirritability developed which responded partially to the intravenous injection of calcium gluconate. Early in January the patient became semistuperous, and on the day before her transfer to Barnes Hospital was found to be unresponsive. Her past history was unknown.

At the time of her admission to Barnes Hospital her temperature was 37.3°C., pulse 110, and blood pressure 140/75 mm. Hg. The patient was semicomatose, lying in bed with her eyes half open and jerking her arms forcefully. She responded to some painful stimuli. There was a foul odor on the breath, dried blood in the right nostril and on the teeth. The skin was mildly icteric. The pupils were widely dilated and reacted to light. Breath sounds were decreased in the lower right lung. A grade 2 systolic murmur was heard at the apex and at the aortic area. The abdomen was distended; the signs of fluid in the peritoneal cavity were detected. The liver was not palpable; the spleen was felt approximately 8 cm. below the left costal margin. Bowel sounds were diminished. A Babinski sign was present on the right. The deep tendon reflexes were reported as being 2 plus and 3 plus and equal bilaterally.

Laboratory studies revealed a hemoglobin of 13.1 gm. per cent; white blood cell count 3,750 per cu. mm. with a differential of 6 per cent bands, 69 per cent segmented neutrophils, 19 per cent lymphocytes and 6 per cent monocytes. Urinalysis revealed a specific gravity of 1.008; protein and sugar negative; 4 to 5 white blood cells and 2 to 3 red blood cells per high power field; urine bilirubin was positive; urine urobilinogen 1.28 Ehrlich units. Stool guaiac positive; blood Kahn reaction negative; nonprotein-nitrogen 17 mg. per cent; blood sugar 140 mg. per cent; serum albumin 3 gm. per cent; serum globulin 2.7 gm. per cent; prothrombin 33 per cent; cholesterol 197 mg. per cent; thymol turbidity 9 units; serum bilirubin 3.9 mg. per cent with direct 1.5 mg. per cent and indirect 2.4 mg. per cent; cephalin cholesterol flocculation 4 plus; alkaline phosphatase 4.7 Bodansky units; SGOT > 200 units; serum glutamic pyruvic transaminase (SGPT) > 112 units; amylase 100 units; Schwartz-Watson reaction

negative; sodium 141 mEq. per L.; potassium 2.4 mEq. per L.; CO_2 18.5 mEq. per L.; chloride 117 mEq. per L.; phosphorus 1.2 mg. per cent; L.E. preparation negative. The initial and two subsequent electrocardiograms were interpreted as showing sinus tachycardia and left ventricular enlargement. Roentgenographic examination of the chest and the abdomen showed cardiomegaly, splenomegaly and the changes of ileus.

On the day after admission a lumbar puncture was performed. The opening pressure was 250 mm. water; the closing pressure was 150 mm. Protein was 33 mg. per cent and sugar 103 mg. per cent. The colloidal gold and Wassermann reactions were negative. Spinal fluid culture showed one colony of white staphylococcus and two colonies of surface fungi, thought to be contaminants. An electroencephalogram was consistent with diffuse organic and/or metabolic basis for symptoms. A neurological consultant did not believe there was any structural brain change and thought there was diffuse brain depression in response to disease elsewhere. Treatment was begun with a broad-spectrum antibiotic, vitamin K, intravenously administered fluids, potassium phosphate, hydrocortisone and a mixture of arginine and glutamine. Within twenty-four hours bowel sounds were heard, flatus was passed, and bowel movements became regular.

Repeat laboratory studies on the second hospital day showed a white blood cell count of 5,950 cells per cu. mm. with a differential of 3 per cent myelocytes, 2 per cent metamyelocytes, 21 per cent bands, 57 per cent segmented neutrophils, 14 per cent lymphocytes and 3 per cent monocytes. Serum calcium and phosphorus were normal; SGOT 1,640 units; SGPT 210 units; electrolytes were normal except for a potassium of 3 mEq. per L. A blood culture and urine culture showed no growth.

During the entire hospital stay the patient's mental status fluctuated between stupor and coma. The results of hepatic function tests remained unchanged. On January 12, 1959, the bromsulfalein retention was 54 per cent; prothrombin 28 per cent; cephalin cholesterol flocculation 3 plus; thymol turbidity 9.6 units; serum albumin 2.6 gm. per cent; serum globulin 2.5 gm. per cent; serum bilirubin 4.3 mg. per cent; alkaline phosphatase 4.5 Bodansky units; serum potassium 2.5 mEq. per L.; CO_2 21.0 mEq. per L.; SGOT 97 units; SGPT 29 units; heterophil agglutinins negative. A persistent proteinuria and microscopic hematuria developed following urethral catheterization. On the sixth hospital day the patient had signs of pneumonia associated with a temperature of 39.5°C. and a white blood cell count of 21,640 cells per cu. mm. Response to penicillin given intravenously seemed good, but the coma became progressively deeper. Four days later congestive heart failure developed. An injection of lanatoside C was given intravenously, but the patient shortly became hypotensive and died quietly.

Blood chemical determinations on the day of death were non-protein nitrogen 90 mg. per cent; sodium 150 mEq. per L.; potassium 5.4 mEq. per L.; chloride 132 mEq. per L. and CO_2 16.9 mEq. per L. During the hospital course the patient maintained a good urine output, varying between 1,000 and 4,900 cc.

CLINICAL DISCUSSION

DR. CARL V. MOORE: The total known duration of this young woman's illness was eight to ten weeks. It was characterized by discomfort in the upper right quadrant, an operation at which a normal gallbladder was removed, signs of progressive hepatic failure and portal hypertension, splenomegaly which was probably congestive in origin, coma, poor response to therapy, pneumonia and terminal cardiac failure. Dr. McAlister, will you discuss the roentgenograms?

DR. WILLIAM H. MCALISTER: The recumbent, short distance roentgenogram taken after expiration created a largely false impression of cardiac enlargement and pulmonary congestion. The bony thorax appeared normal. There was some pleural thickening extending into the minor fissure; I am not sure whether this was recent or old. The abdominal roentgenogram showed the spine to be normal. The psoas shadows were seen. There was some dilatation of both the large and small bowel. Minimal separation of the loops of small bowel raised the question of ascites. The liver did not appear to be enlarged. There was a large, soft tissue mass in the upper left quadrant, displacing the splenic flexure, left kidney and stomach. This was perfectly consistent with an enlarged spleen. The radiographic detection of splenic enlargement was largely a subjective one based on the displacement of these structures and elevation of the left hemidiaphragm. A rough guide in the determi-

nation of normal splenic size on abdominal roentgenograms is by measuring the spleen's diameter 2 cm. above the inferior pole. A measurement greater than 5.4 cm. suggests splenic enlargement.

DR. MOORE: Dr. Shank, what kind of jaundice do you think this patient had and what kind of damage to her liver?

DR. ROBERT E. SHANK: To me the evidence suggests parenchymatous jaundice, or a necrotic process in the liver. Various causes of necrosis have to be considered here. One was apparently proposed during the time of her admission; this was viral hepatitis.

DR. MOORE: You think she had a parenchymatous type of jaundice and suggest that there is evidence of hepatic cell necrosis?

DR. SHANK: I would have to interpret the total data that way, yes.

DR. MOORE: Before we discuss the differential diagnosis, I thought it would be of interest to have Dr. Morrison briefly review some of the new approaches being made to determine the susceptibility of different portions of the liver lobule to injury.

DR. GEORGE R. MORRISON: In an attempt to gain information regarding the pathogenesis of liver cell injury, Dr. Shank and other members of the Department of Preventive Medicine have concentrated upon the biochemical susceptibility of normal liver cells to injury. We have been particularly interested in explaining why pathologic lesions in many types of hepatic injury are characterized by a zonal distribution within the hepatic lobule.

Prior to 1950, emphasis was placed upon the influence of blood supply in the physiology of the lobule. It was held that the periportal cells are in a more favorable position to receive oxygen, nutrients and toxins entering the lobule from the hepatic arterial and portal blood, while the centrolobular cells receive what is left over as well as the byproducts of metabolism released from the periportal cells.

In the past decade, however, increasing emphasis has been placed upon the differences between the cells themselves within the hepatic lobule. This approach holds that cells in adjacent areas of the hepatic lobule differ in their capacity to fulfill specific roles in metabolism. Another approach to the pathogenesis of liver disease is an old one, based upon the knowledge that even in normal livers deposits of glycogen are greatest in periportal areas, while the deposition of lipid is likely to be greatest in the central areas. Newer achievements in the fields of submicroscopy and histochemistry have offered support for this approach. The intralobular distributions of mitochondria and the phosphatases are well known. Now, with evidence accumulating that hepatotoxic agents and nutritional deficiencies act by interfering with carbohydrate, protein or fat metabolism, an increasingly fruitful unification of our knowledge is anticipated with this approach.

Prior to our work, all the studies demonstrating that the activity of an enzyme frequently differs from one zone to another within the same hepatic lobule, utilized the histochemical staining technics. Recently Dr. Novikoff* summarized these results. Besides being semiquantitative, however, methodological restrictions have seriously limited the number of enzymes which can be studied with the staining technics. On the other hand, the histochemical methods developed by Dr. O. H. Lowry† make comparisons of enzyme activity from tissue sections incubated in separate microtest tubes. Besides being quantitative, analyses of numerous enzymes are possible, even with single liver cells.

The enzymes we have studied are phosphoglucose isomerase (PGI), glucose-6-phosphate dehydrogenase (G-6-PDH), lactate dehydrogenase (LDH), isocitric dehydrogenase (ICDH), malic dehydrogenase (MDH) and the transaminases. In addition, alkaline phosphatase, total protein and desoxyribose nucleic acid (DNA) have been studied. The data we have obtained on normal man and normal rat liver enzymes have been related to a desoxyribose nucleic acid baseline.

In summary, in both rat and man, those enzymes which participate in aerobic systems, that is, isocitric dehydrogenase, malic dehydrogenase, and glucose-6-phosphate dehydrogenase, have relatively greater activities in the centrolobular area of the hepatic lobule when compared with the enzymes which are able to maintain function under more anaerobic conditions. The latter group, phosphoglucose isomerase, lactic dehydrogenase, and glutamic pyruvic transaminase, have considerably greater periportal activities. The fact is clear, however,

* NOVIKOFF, A. B. and ESSNER, E. The liver cell. *Am. J. Med.*, 29: 1, 1960.

† Department of Pharmacology, Washington University School of Medicine, St. Louis, Missouri.

that enzyme activity varies throughout the liver lobule.

We do not attempt to draw conclusions at the present time, but merely wish to emphasize that it does appear that further studies with these methods will contribute importantly to our understanding of the susceptibility of normal cells in various areas of the hepatic lobule to a variety of types of injury. It is our hope and intent in the future to apply these studies to the experimental animal and to man with a variety of types of liver diseases.

DR. MOORE: While these comments do not help us understand the problem presented by this young woman, they indicate the direction in which our thoughts may take us several years from now.

Dr. Shank, may we get back to the differential diagnosis? When I interrupted you, you had just mentioned the possible diagnosis of viral hepatitis.

DR. SHANK: This is certainly a diagnosis that should be considered here. But in recording this opinion I would like also to mention a number of things that disturb me a bit in applying this diagnosis. One is the fact that the first manifestation of hepatic damage was ascites; it was not until later that jaundice was observed and that there was other evidence of hepatic damage.

DR. MOORE: The discomfort in the upper right quadrant may have been the first manifestation.

DR. SHANK: Perhaps we should consider the possibility that the patient had anicteric hepatitis at the time of surgery and that this was of sufficient severity for ascites to rapidly occur after surgery. I would also like to point out, as a possible problem in considering a diagnosis of viral hepatitis, the fact that the spleen was fairly markedly enlarged. In fulminant hepatitis, that is with death occurring within ten days, the spleen although enlarged at autopsy is usually not palpable, or if palpable it is not of the size described here. This patient survived for a somewhat longer period, which would put this disorder in the category of subacute hepatitis. In subacute hepatitis with death occurring several months after the onset of the disease, pronounced splenomegaly is more common.

DR. MOORE: Dr. Sherry, Dr. Shank has emphasized that some of the clinical manifestations shown by this young woman are unusual or atypical for viral hepatitis. The principal evidence for hepatic cell necrosis was the transaminase values which changed in a rather peculiar manner. Will you interpret these for us, and tell us in particular whether you think that an elevated transaminase level of 1,640 units, falling within a few days to 97, could be explained by any other kind of intra-abdominal lesion.

DR. SOL SHERRY: The persistent elevation of the transaminase levels over an extended period of time, including an elevated level on the patient's previous admission at another hospital, plus the very high level of 1,640 units, would suggest hepatic injury in this patient. On the other hand, the level of the transaminase may be influenced in this complicated case by the presence of many other extrahepatic factors, such as myocardial disease, possible biliary tract involvement, and perhaps other organ system involvement as well. Therefore, the interpretation of the transaminase levels, in terms of the extent of the hepatic injury, is impossible in this patient.

A number of investigators have been concerned with the lack of specificity of the transaminase in terms of its organ source, and are trying to develop methods to improve our interpretation of the transaminase. One such approach recently has been reported by Wroblewski and his associates.* They studied the nature of the various lactic dehydrogenases which are present in normal plasma and pointed out that five different lactic dehydrogenases or isoenzymes are present. These can be separated by starch-gel electrophoresis and independently analyzed. Since the myocardium is richest in the fastest moving components, whereas liver is richest in the slowest moving components, they have been able to distinguish quite clearly (at least in their preliminary observations) when elevations in lactic dehydrogenase are due to myocardial infarction or to hepatic disease. They also pointed out that the changes occurring following myocardial infarction last much longer than indicated by the usual total assay for the enzyme. However, the technic at present seems to be more of a research tool than one readily applicable for use in a general clinical laboratory.

Another approach under active exploration is the development of specific inhibitors, e.g., specific antiserums for each of the isoenzymes. In this way one could determine when the elevation in transaminase levels is due to hepatic origin or

* WROBLEWSKI, F., ROSS, C. and GREGREY, K. Isoenzymes and myocardial infarction. *New England J. Med.*, 261: 531, 1960.

to myocardial infarction or to other organ involvement.

DR. MOORE: Will such elevated levels ever be found in acute pancreatitis?

DR. SHERRY: We have seen patients with acute pancreatitis, usually the type associated with transient biliary tract obstruction, in whom the levels of transaminase were several hundred units and then rapidly fell. The elevated transaminase level did not bear a close relationship to the serum amylase level. The pathogenesis of the elevation in transaminase levels was not clear, and it has been noted by others that in pancreatitis considerable elevations in transaminase levels can occur, but they are inconstant.

DR. SHANK: I would just like to point out that there is one other important evidence of hepatic parenchymal damage—the prolonged prothrombin time.

DR. MOORE: And the lack of response to vitamin K therapy.

Dr. Berg, you saw this patient when she was alive; do you think her neurological changes were consistent with a diagnosis of hepatic coma? Do you have any other comments to make about the neurological state?

DR. LEONARD BERG: Her neurologic state certainly was consistent with hepatic coma in its features of early delerium lapsing into a coma, with the muscular hyperirritability, hyperreflexia, rhythmical jerking movements, and the diffusely slow electroencephalogram. The only neurologic point that deserves the least question is the elevated spinal fluid pressure. It did not fall much after the removal of 15 cc. of fluid. The high initial pressure might well have been related to rigidity or involuntary movement at the time of the spinal tap.

DR. MOORE: Dr. Karl, you took care of this patient and arranged for her to be given arginine and glutamine shortly after she was transferred to your service. Would you evaluate the effectiveness of these two substances in the treatment of hepatic coma?

DR. MICHAEL M. KARL: The administration of both of these substances is predicated on the known changes that take place in ammonia metabolism in hepatic failure. Excess ammonia may be inactive when it combines with glutamic acid in the presence of glutamic dehydrogenase to form glutamine. The administration of glutamic acid may also increase the rate of amination, amidation and transamination, all of which are methods of disposing of blood ammonia. Lastly, the administration of arginine by increasing the available substrate, may accelerate the synthesis of urea from ammonia; not only in the liver but also in the brain. While theoretically on firm ground, the administration of these substances has not produced consistent results in this type of patient. I would summarize by saying that I think the administration of such intermediary metabolites is probably useful when hepatic coma is induced perhaps by exogenous factors, rather than by primary liver failure.

DR. MOORE: How did you explain the very low serum potassium and phosphorous levels?

DR. KARL: The very low serum potassium level, of course, has been noted in patients with liver coma. This patient was given diuretics and steroids prior to being brought over to this hospital, both of which can produce hypokalemia. Independently of the administration of diuretics, hypokalemia has been described in association with alkalosis.

DR. MOORE: One of the things which bothered everyone was the possibility that there may have been a surgical accident at the time of the operation which was responsible for the subsequent ascites, the tremendous enlargement of her spleen; perhaps also for the hepatic failure. I have asked Dr. Moyer if he would tell us what kind of damage the surgeon is likely to do under these circumstances.

DR. CARL A. MOYER: The first accident that may happen is to operate upon a subject who has hepatitis and thereby activate the hepatitis anew. This is an accident related to error in diagnosis. This may have happened here. Secondly, of course, is inadvertent mayhem. There are three types of this. The first and most frequent one is ligating the common duct. This, of course, precipitates what might be termed total jaundice. With certainty this did not occur in this case because the patient's level of bilirubin was not at all consistent with ligation of the common duct, and the rest of the picture does not fit it; the hepatomegaly and the ascites especially. The next accident, although rather infrequent, is placing a ligature on the hepatic artery proper, or its right branch. Most patients recover, so it seems, from the ligature of one branch of the hepatic artery. However, death has followed the ligation of only the right hepatic artery. Why is ligation of the hepatic artery and especially the division of the right possible? The cystic artery comes off the right hepatic artery

or the anteria propria while the artery is still to the left of the portal vein and the common bile duct. In these cases it is fairly easy to pick out the cystic artery. Unfortunately, however, nature frequently mixes the relationships of the cystic artery to the hepatic artery and one of the variants in take-off of the cystic artery that is fairly frequent is its origin from the right hepatic artery, very close to the gallbladder or cystic duct, after the right hepatic artery has passed from the left to right behind the common hepatic duct. In cases such as this, traction upon the cystic duct inadvertently pulls the right hepatic artery into such a position that a ligature is easily put around what appears to be the cystic artery but in reality is the right hepatic artery. This could happen rather frequently. During the last year it could well have happened three times on the surgical services of Barnes Hospital had the residents not exercised great caution in ligating the cystic artery and picked these anomalies up. One resident actually had a ligature placed about the hepatic artery and was ready to tie it when he thought he had better take another look. Much more rarely, the hepatic artery proper is in such a position as to be inadvertently tied off, but it may be injured as a consequence of the accident of losing control of the stump of the cystic artery. A hemostat is blindly placed in the region of the bleeding and closed and everything that is by chance inside of it is crushed, and is subsequently secured with ligatures. This is not done by the man who has taken the precaution of being sure that the foramen of Winslow is open so that, should uncontrolled bleeding occur from an escaped cystic artery, he may cut off flow through the hepatic artery by finger pressure and then find the end of the cystic artery which may then be readily and safely secured. The patients I have seen in whom this accident has happened died of acute hepatic insufficiency without ascites and without splenomegaly.

The third accident, namely injury to, or occlusion of, the portal vein, is extremely rare. Occasionally a hole may be made into the portal vein inadvertently and in sewing it up or trying to fix it, the vein's lumen is so compromised that thrombosis occurs. How long does the person usually live after a ligature is put about or clot occludes a virgin portal vein? Usually hardly more than six hours, because the intestinal veins swell up with exorbitant rapidity, the blood pressure drops, blood and plasma are lost at a rate that can not be kept up with, and death soon occurs, at times within the hour. I think that the actual ligature or postoperative thrombosis of an injured portal vein is not a possibility in this case. From what I have seen of the protocol I would judge that the surgeon had little to do with this patient's death.

DR. MOORE: Would you care to tell us why you think the spleen was so enlarged?

DR. MOYER: Of course, it fits a slowly progressive portal venous obstruction, such as by clots.

DR. MOORE: But the surgeon would not have anything to do with that?

DR. MOYER: Not knowingly, or unknowingly. However, unknown peculiarities of nature sometimes lead to thrombotic portal venous obstruction. It has followed operations upon the biliary tract just as it has followed operations upon other organs within the abdomen. Most often we cannot relate it to anything that we have done, it just occurs. Of course, all of you know that after an operation, or after an injury, venous thrombosis anywhere in the body is more frequent than it is in a normal person at home or walking the street.

DR. MOORE: Since the surgeon did not mention the size of the spleen at the time of operation, we have to assume that the splenomegaly was probably of recent origin.

Dr. Smith, unless I postulate that this woman had at least a partial occlusion of the portal vein, I have a hard time explaining the chain of events. I do not see how one can explain the rapid onset of ascites and the tremendous splenomegaly on the basis of acute viral hepatitis. Can you postulate any likely mechanism for the ascites in this patient that is not related to partial obstruction of the portal vein system?

DR. JOHN R. SMITH: Perhaps it might be well to reexamine the various types of ascites. The most striking ascites, and the most common, results from gross distortion of the liver in the course of cirrhosis of the liver. A similar type of ascites occurs in persons with marked liver congestion from congestive heart failure. Now, this type of ascites is usually somewhat slow in onset; it may reach prodigious size. It appears to be a distillate, so to speak, of liver lymph which leaks from the liver surfaces and is then diluted in the peritoneal cavity.

On the other hand, another form of ascites that has been much more difficult to study results from portal obstruction. It is more serious than the ascites of cirrhosis. It seems often to occur

in inverse proportion to the amount of collateral circulation that develops between portal and systemic veins. This ascites may in large part subside, or at least not become very severe. Perhaps in such a case, or in this case for that matter, the source of continuing ascites may be from the tissues which drained into such portions of the portal vein as may have been completely obstructed. In other words, this type of ascites is rather like edema.

The ascites of infection, of course, is usually accompanied by signs of infection and may be voluminous. Fluid from malignancy of the peritoneum, or malignancies of the bladder, and similar lesions is encountered less frequently. In this case, since the spleen was really quite large and there was an ascites that did not reach large proportion, it is suggestive to me of an obstruction in the portal vein in or below the liver, but involving the splenic vein. Ordinarily, the spleen does not become this large in congestive heart failure. Usually hepatic circulatory obstruction is not complete in congestion and blood flow is slowed. This situation suggests that there was probably complete splenic venous obstruction, and the spleen became very large. The liver did not become large itself, because it was not the subject of congestion, or it tended to contraction because of diminution of hepatic blood flow, or from liver cell failure and necrosis.

DR. MOORE: Dr. Morrin, could you tell us briefly whether you think this patient had the so-called hepatorenal syndrome? Can one explain the electrolyte changes on that basis? How do you account for a rise in the serum chloride to 132 mEq. per L., and of the sodium to 150 mEq. per L.?

DR. PETER A. F. MORRIN: I do not think we have any good evidence for the hepatorenal syndrome in this case. The hepatorenal syndrome is a very vague entity, about which there is still no clear-cut understanding. Most of these cases are characterized by a decreasing urine volume, usually associated with ascites and low serum sodium levels. The urine from these patients is frequently concentrated and contains little or no sodium, in contrast to cases of acute tubular necrosis in which the urine is isotonic with plasma and usually contains large amounts of sodium. This woman had a good urine output until the day prior to death. This, I believe, would be against the more common form of so-called hepatorenal failure. The rise in non-protein nitrogen to 90 might be explained by extrarenal causes. In some patients a progressive rise in non-protein nitrogen or blood urea nitrogen develops in association with good urine output and these differ from the more common form of hepatorenal failure in which oliguria is a prominent feature. The present case may belong to this other category, although I will be surprised if the patient's kidneys show significant histological lesions.

As regards the electrolytes, I think that the sodium level of 152 at the time of death can be attributed to the administration of sodium in excess of the excretion. I do not think it implies a primary renal defect. It is worth noting that she may have received quite considerable amounts of sodium ion in the form of sodium gluconate. The low potassium level, as Dr. Karl has remarked, is probably to be attributed to (1) inadequate potassium intake during the period of her coma, and (2) the alkalosis which is frequently seen in these patients.

DR. MOORE: I have not said anything about the high blood sugar value, because the blood was drawn while glucose was being given intravenously.

Dr. Reichlin, could you say something about the possible relationship of the hyperchloremia to the neurological problem?

DR. SEYMOUR REICHLIN: There is a great deal of recent experimental data concerning central nervous system regulation of electrolyte and water metabolism, particularly of aldosterone and vasopressin release. However, in this case it seems more reasonable to attribute the patient's electrolyte difficulties to her inability to respond to normal thirst sensation and also to abnormal renal function.

DR. KARL: I would like to point out that this patient received arginine glutamate rather than sodium glutamate. On reviewing the type of fluid administered I do not think that sodium could account for these levels, since most of the fluids were glucose in water.

DR. MOORE: Most of the parenteral fluid was glucose and water, rather than glucose and saline.

DR. KARL: I would like to suggest that this is the hypernatremia sometimes noted in central nervous system disturbances of various types, the mechanism of which is not fully understood, but which may be related to damage in the hypothalamus.

DR. MOORE: Do you know what was found at the time of autopsy?

DR. KARL: No sir.

DR. MOORE: Would you care to tell us what your final diagnosis is?

DR. KARL: To me the presence of pain in the upper right quadrant and a non-visualizing gallbladder, with a normal gallbladder found at operation, suggests severe liver damage must have been present prior to the cholecystectomy. Accordingly, I would like to suggest that this patient initially had anicteric viral hepatitis. The trauma of cholecystectomy and anesthesia, with all due deference to Dr. Moyer, precipitated subacute hepatic necrosis which accounted for her death. The presence of so large a spleen may have been caused by a complicating thrombosis of the portal vein. This, however, is an extremely rare complication, and I really do not think it was present in this patient.

DR. MOORE: I think Dr. Karl has stated clearly the most likely diagnosis, and I am in agreement.

DR. SHERRY: Dr. Smith implied that, if a thrombosis was present, it was restricted to the extrahepatic area. I would suggest that if a thrombosis was present, it probably also extended up into the liver in order to account for the extensive hepatic dysfunction which the patient presented.

DR. MOORE: That is a very good point; one that Dr. Moyer and I have already discussed. Would you be in agreement with that, Carl?

DR. MOYER: Yes, essentially. It is much more likely that the severe hepatic insufficiency be associated with clotting of terminal branches of the portal vein, but in one case that I know about the thrombosis did not extend into the hepatic venous radicles, but stopped just short of them, and yet there was almost complete disintegration of the liver and the person died of acute hepatic insufficiency.

PATHOLOGIC DISCUSSION

DR. JOE W. GRISHAM: I would agree that the surgeon made at least two mistakes, one in not performing a liver biopsy and another in incorrectly interpreting the gross appearance of the liver.

This patient was a well developed, white woman, who weighed 56 kg. and measured 173 cm. in length. There was moderate jaundice of the skin and the sclerae and there was a well healed, 21 cm. rectus incisional scar in the upper right quadrant. The peritoneal cavity contained 750 ml. of clear yellow fluid. There were no pleural or pericardial effusions. Over the serous surfaces of most of the viscera there were a few petechiae.

The liver was shrunken in size, weighing 630 gm., which accounted for the fact that it was not interpreted as being enlarged on the roentgenogram. The capsular surface was markedly nodular. On cut surface there were parenchymal nodules which varied in size from 3 mm. to 3 cm. in diameter. (Fig. 1.) Separating these nodules were grayish bands of connective tissue which varied in width from a few mm. to 2 to 3 cm. The nodules were variegated in color, generally being a rather tawny orange, but some were deep brown and appeared to be hemorrhagic. Others were depigmented and interpreted as being necrotic. The extrahepatic biliary system was intact except for the surgical absence of the gallbladder. The hepatic ducts and common bile duct were patent throughout.

Histologically the liver appeared as might be expected. There were bands of connective tissue of variable width, some very broad and others quite narrow. (Fig. 2.) Regenerative nodules varied considerably in size and many of the larger were multilobular. From a morphological standpoint this conforms to so-called postnecrotic cirrhosis and histologically meets Steiner's criteria* for this same type of cirrhosis in that in several fibrous bands three or more portal structures were apposed. (Fig. 2.) This process had probably been going on for some time. In the fibrous bands, the connective tissue stained in a manner indicative of mature collagen. This is more than would be expected from a recent collapse of tissue. There was a variable, but generally sparse chronic inflammatory infiltrate in the fibrous bands. (Fig. 3.) Bile ductules or cholangioles showed evidence of proliferation and many of these contained bile casts. Cholestasis was also marked within the canaliculi between adjacent parenchymal cells. Parts of some regenerative nodules were necrotic, probably on the basis of vascular insufficiency. This fact may help explain the serum enzyme findings.

From the morphologic appearance of this liver we cannot tell you the etiologic agent responsible. It could be any of the numerous stimuli which result in necrosis of hepatic parenchyma. We have no evidence of contact with any toxic agent, but neither do we have

* STEINER, P. E. Precision in the classification of cirrhosis of the liver. *Am. J. Path.*, 37: 21, 1960.

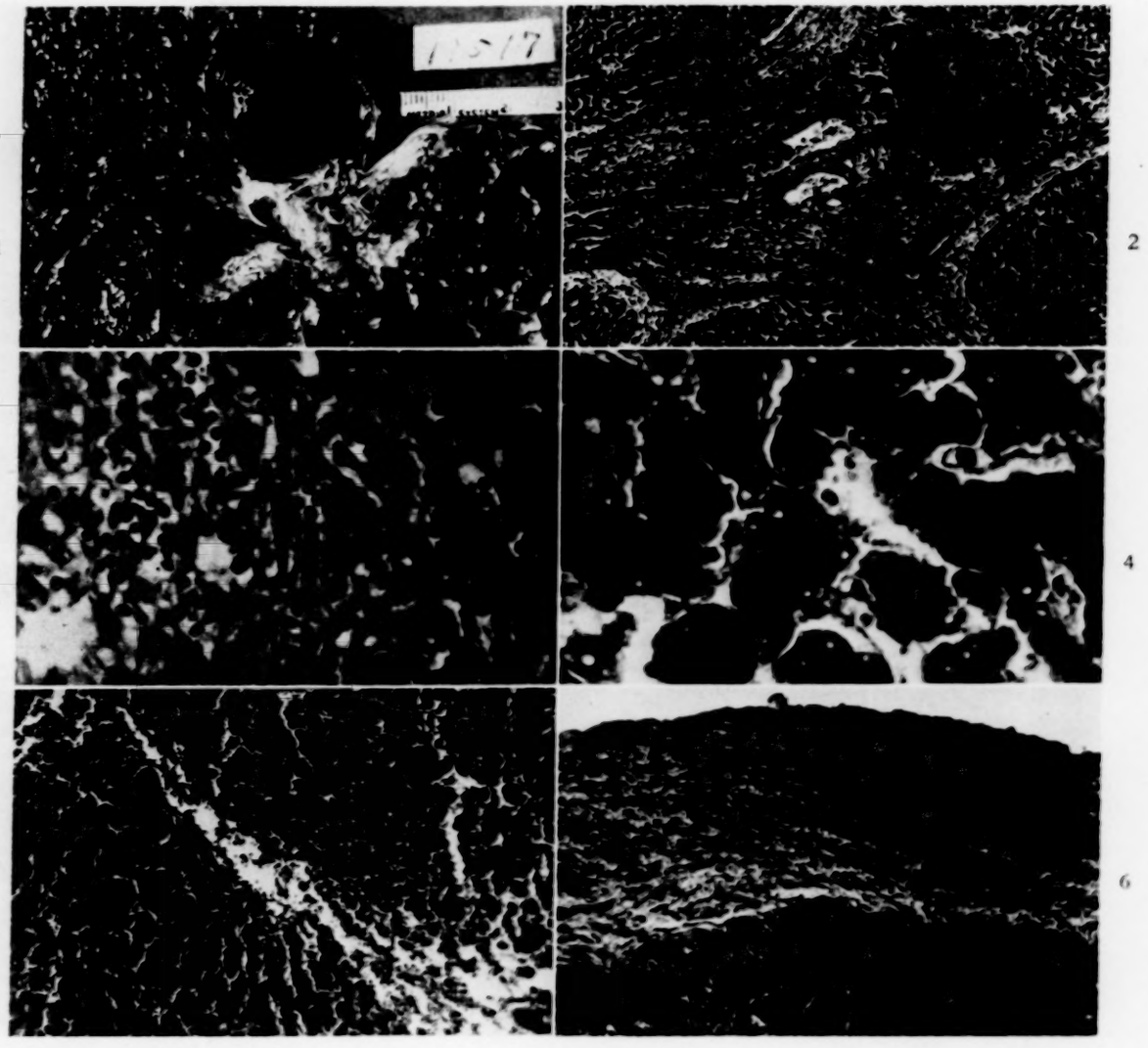

FIG. 1. The cut surface of the liver illustrating the wide variation in the size of regenerative nodules and fibrous bands.

FIG. 2. Fibrous bands between regenerative nodules varied greatly in width and some contained several portal structures in apposition. Masson trichrome stain, original magnification × 75.

FIG. 3. Sparse nonspecific chronic inflammatory infiltrate in the fibrous bands. Hematoxylin and eosin stain, original magnification × 500.

FIG. 4. Canalicular cholestasis in centers of regenerative nodules. Hematoxylin and eosin stain, original magnification × 500.

FIG. 5. Area of necrosis (upper right) in a regenerative nodule. Hematoxylin and eosin stain, original magnification × 75.

FIG. 6. Marked fibrous intimal thickening of the portal vein which frequently accompanies portal hypertension. Hematoxylin and eosin stain, original magnification × 75.

any history of contact with jaundiced people. However, as Dr. Shank has mentioned, anicteric hepatitis is much more frequent in occurrence than the icteric variety and it is entirely possible that this patient may have had anicteric viral hepatitis which progressed to postnecrotic cirrhosis. In this regard I might mention that Dr. Gerald Klatskin at Yale has collected several case reports of patients with anicteric hepatitis in whom cirrhosis developed.* He has picked up these cases because liver biposies are performed

* KLATSKIN, G. Subacute hepatic necrosis and post necrotic cirrhosis due to anicteric infections with the hepatitis virus. *Am. J. Med.*, 25: 333, 1958.

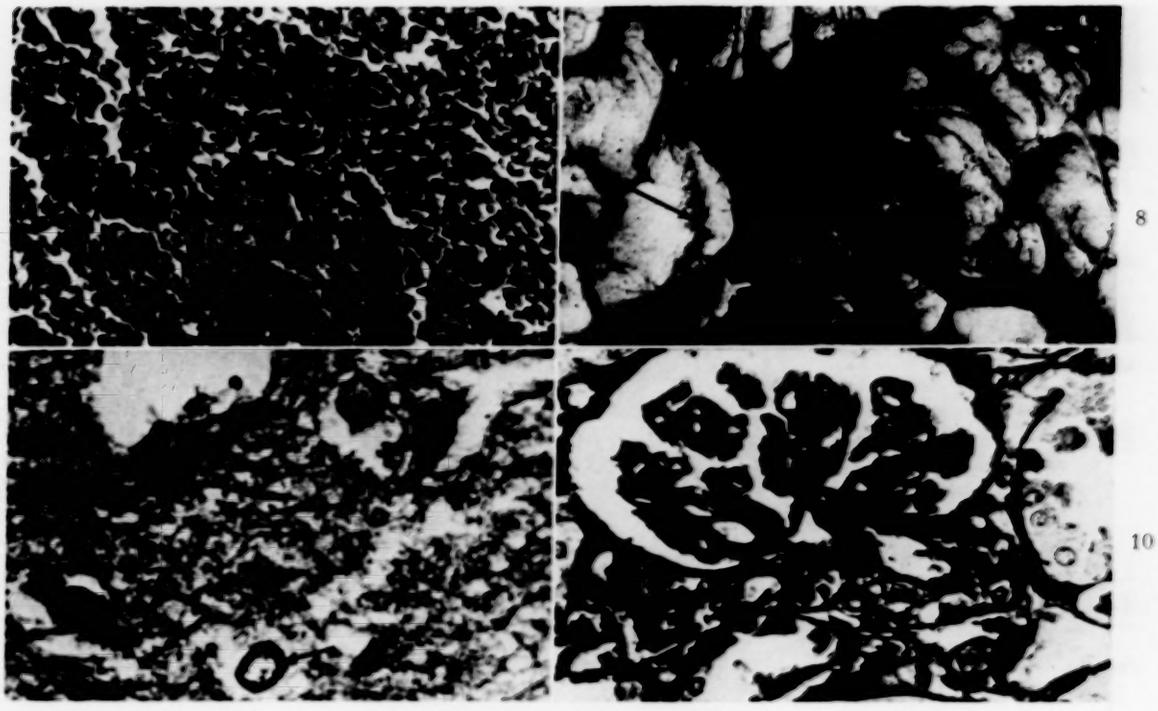

FIG. 7. Fibrosis of the splenic pulp. Masson trichrome stain, original magnification × 300.

FIG. 8. The base of the brain showing bilateral uncal grooving (arrows).

FIG. 9. Vacuolated astrocyte nuclei (arrows) from the basal ganglia. The dark nuclei represent more normal astrocytes. Hematoxylin and eosin stain, original magnification × 600.

FIG. 10. The arterial pole of a glomerulus showing eccentric hyperplasia and hypergranularity (arrow) of the juxtaglomerular cells. There was focal hyperplasia of the zona glomerulosa of the adrenal. Periodic acid-Schiff stain, original magnification × 500.

on all patients who come to the Yale Medical Service with any evidence of hepatic disease. In the nine cases that he has reported, the initial symptoms were often vague and some of the patients were operated upon for suspected lesions of the gallbladder. It is very difficult to age the cirrhotic process from morphologic criteria in the case under discussion but it could easily have occurred in the time interval since vague symptoms were first noted. In Dr. Klatskin's cases the time interval from initial entry to the hospital to termination or hepatic failure varied from five and a half months to four years and jaundice did not occur until the cirrhosis was well developed.

The hepatic artery was not abnormal, but the portal vein and its major tributaries were greatly dilated. There were fibrous intimal plaques on the wall of the portal vein reflecting an increased portal vein pressure. (Fig. 6.) There were varices of the distal and mid-esophagus which showed no evidence of rupture. The spleen was enlarged and congested. It weighed 480 gm. The follicles were inapparent. Histologically, there was an increased amount of connective tissue between the sinusoids. (Fig. 7.) This increase in connective tissue does not appear until the portal hypertension has been present for some time.

The brain weighed 1,480 gm. It was edematous with definite bilateral uncal grooves. (Fig. 8.) There was increased prominence of oligodendroglial cells. Evidence from electron microscopy indicates that these cells are responsible for the inhibition of water in cerebral edema. Many astrocytes in the basal ganglia, cortex and brain stem contained ballooned vacuolated nuclei with peripheral margination of chromatin. (Fig. 9.) Similar alterations in astrocytes have been reported in the brains of patients dying in hepatic coma.* They were most numerous when coma was prolonged.

The kidneys weighed 170 gm. each. There was

* ADAMS, R. D. and FOLEY, J. M. Metabolic and toxic diseases of the central nervous system. In: Proceedings of the Association for Research in Nervous and Mental Diseases, p. 32. Baltimore, 1952. Williams & Wilkins Co.

a fine granularity of the surface with other deeper, pitting scars which histologically represented foci of chronic pyelonephritis. There was hypergranularity and hyperplasia of the juxtaglomerular cells of the kidney. (Fig. 10.) This finding is difficult to correlate with the elevated plasma sodium values. The granularity of the juxtaglomerular cells has been shown to correlate inversely with the sodium level and the patients with the greatest juxtaglomerular granularity and hyperplasia have been cirrhotic subjects with ascites.* There is considerable evidence that this apparatus is responsible for the trophic hormone for aldosterone and, in keeping with the state of the juxtaglomerular apparatus, there was focal hyperplasia of the zona glomerulosa of the adrenal cortex.

The lungs were congested, but only slightly edematous. There was a little proteinaceous exudate in the alveolar spaces and there were focal areas of atelectasis. The heart was not enlarged by weight but the chambers were uniformly dilated. There were subendocardial and subepicardial petechiae and focal areas of sparse chronic inflammatory cells. An interesting incidental finding was ectopic pancreas in the first part of the duodenum associated with acute inflammation. There was also focal fat necrosis of the body of the main pancreas.

In summary then, our primary final diagnoses were postnecrotic cirrhosis with recent focal necrosis and cholestasis; fibrocongestive splenomegaly with dilatation and phlebosclerosis of the portal, mesenteric and splenic veins; varices of the esophagus; ascites; edema of the lower extremities; cerebral edema with uncal grooving; encephalopathy of hepatic failure; pulmonary congestion; focal myocarditis; petechiae of the epicardium and endocardium; and surgical absence of the gallbladder with healed right rectus abdominal scar.

* Pitcock, J. A. and Hartroft, P. M. The juxtaglomerular cells in man and their relationship to the level of plasma sodium and to the zona glomerulosa of the adrenal cortex. *Am. J. Path.*, 34: 863, 1958.

DISCUSSION

Dr. Moore: Dr. Karl, from your examination of the record at the other hospital, can you tell us if any hepatic function tests were performed prior to the time of operation?

Dr. Karl: The only hepatic function tests in the record are those in the protocol, the elevated SGOT levels and the positive cephalin cholesterol flocculation.

Dr. Moore: After the operation?

Dr. Karl: These were after the operation, yes.

Dr. Moore: Dr. Moyer, the American College of Surgeons has established regulations stipulating that certain minimal clinical and laboratory data must be obtained on every patient prior to operation. Have we not reached the point when any patient subjected to cholecystectomy should have some preoperative evaluation of hepatic function?

Dr. Moyer: I agree with you completely.

Case Reports

Functional Islet Cell Carcinoma Metastasizing as Spindle Cell Tumor*

A Possible Clue to the Riddle of Extrapancreatic Tumors Causing Hypoglycemia

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SPORADIC but increasing interest has been directed in the last three decades toward the intriguing subject of extrapancreatic tumors associated with hypoglycemia. The earliest case report was that of Anderson [*1*] in 1930, of a carcinoma of the left adrenal cortex causing fatal hypoglycemia. Five more examples of such extrapancreatic neoplasms of epithelial origin have been collected from the literature [*2–5*]. These have all been either adrenal cortical tumors or pseudomyxomas in the abdomen.

More attention has been directed toward bulky spindle cell tumors, variously called "fibromas" and "sarcomas," and presumably of mesodermal origin, in association with hypoglycemia. The first example of this genre, published soon after Anderson's report, was cited by Doege [*6*]. He records the history of a sixty-one year old man who suffered from recurrent hypoglycemia with irrational behavior that responded to rectal administration of glucose. The patient was cured after a four and a half pound fibrosarcoma was removed from the left side of his mediastinum. In all, we have found twenty-two cases of extrapancreatic spindle cell tumors associated with hypoglycemia [*6–24*]. Most of the tumors were discovered in the retroperitoneal area or thorax. Removal of the tumor resulted several times in the prompt relief of hypoglycemic symptoms.

There are many current theories regarding the mechanism whereby large spindle cell tumors induce low blood sugar. Sellman et al. [*21*] have listed the following eight possibilities: (1) tumor production of material stimulating insulin production by the pancreas; (2) abnormalities of an insulinase system; (3) tumor causing hepatic disease; (4) starvation; (5) adrenal insufficiency; (6) tumor storage and consumption of carbohydrates; (7) tumor production of a non-insulinase-inhibiting, hypoglycemia-producing substance different from insulin; and (8) tumor production of insulin or insulin-like material.

With regard to the last possibility, Skillern et al. [*23*] believe that in their two cases islet cell tumors with metaplasia to a spindle cell appearance, but still insulin-secreting, were represented. Indeed, a Gomori stain of retroperitoneal fibrosarcoma in these cases revealed beta granules. (The significance of a Gomori stain on tumors of the soft tissue has been questioned by Miller et al. [*13*] because mast cells in such tumors also take the stain.) Unfortunately, insulin assays were not carried out in Skillern's cases, and attempts at assay by Howard [*12*], Pedersen, Lund and Ringsted [*16*], Scholz, Woolner and Priestly [*19*], Seckel [*20*], and Sellman et al. [*21*] failed to demonstrate insulin within the tumors in their cases. On the other hand, August and Hiatt [*9*] have emphasized the technical difficulties which vitiate successful insulin assay under such circumstances. In their case, an eighty-two year old

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woman who was relieved of hypoglycemia after the removal of a 1,370 gm. fibrosarcoma from the left chest cavity, they demonstrated a concentration of insulin in the tumor which was three times that of a normal pancreas. Miller et al. [*13*] also were successful in finding insulin activity in one of the two tumors that they tested.

A valuable bit of collateral evidence in support of the theory that spindle cell tumors have the potential to produce insulin would be the demonstration that islet cell carcinomas actually can undergo metaplasia to spindle cell tumors. A patient is reported on herein to illustrate that this does occur: a patient with a typical functional islet cell carcinoma in the pancreas had metastases of typical spindle cell appearance.

Hypoglycemia resulting from a metastatic islet cell carcinoma has been known to occur ever since the report by Wilder et al. [*25*] in 1927. However, we believe the present report to be the first of an islet cell tumor metastasizing as a spindle cell tumor. We cite it because of its bearing on the problem of extrapancreatic tumors and hypoglycemia.

CASE REPORT

The patient, a fifty-four year old man, had a cholecystectomy performed in January 1955 for chronic cholecystitis with stones. One year later he began to lose weight and became jaundiced for the first time. At operation in March 1956 a stricture was found at the lower end of the common bile duct. Choledochojejunostomy was performed. Observers thought that the liver appeared normal, but that the pancreas was fibrotic and indurated; no tumor could, however, be demonstrated. Biopsy of several enlarged mesenteric lymph nodes revealed only reactive hyperplasia.

The icterus subsided following the operation, and the patient felt well for a short time. The respite ended with the onset of recurrent and severe hypoglycemic attacks. Fasting blood sugar determinations were 54 and 46 mg. per cent. Four diastase determinations ranged between 40 and 64 units. An upper gastrointestinal roentgenographic examination suggested extrinsic pressure on the lower part of the stomach and duodenal loop. Interval feedings were ineffective in relieving the patient's symptoms. He was transferred to the Jewish Hospital of St. Louis for further study. A tender, nodular liver was now palpable down to the umbilicus. Biopsy of the liver revealed a metastatic tumor composed of compactly arranged spindle cells. Fasting blood sugars now ranged from 21 to 49 mg. per cent. An intravenous glucose tolerance test showed a fasting level of 32 mg. per cent, 98 mg. per cent at a fourth of an hour, 62 at a half hour, 54 at one hour, and 32 at two hours. Radioactive iodine uptake was normal. Steroid determinations in the urine were normal and showed a normal response to an eight hour intravenous drip of ACTH. Orally administered cortisone in doses of 200 to 400 mg. daily relieved the patient of his hypoglycemic symptoms. After five days of therapy his fasting blood sugar level was 69 mg. per cent. However, his condition continued to deteriorate and he died one month later.

Postmortem examination of the pancreas revealed a hard, white, fibrotic gland from which the normal lobular architecture had disappeared. The pancreatic artery showed no gross alteration, but the splenic vein was thrombosed in almost its entire course behind the pancreas. The gallbladder was absent. The common duct, about 2 to 3 cm. from its origin, was anastomosed to the jejunum by a Roux-en-Y type anastomosis, which was healed, intact and patent. The liver showed numerous gray and white tumor nodules, ranging from a few millimeters to 6 cm. in diameter. There were several hemorrhagic areas. The duodenum was densely adherent to the pancreas. There was no other evidence of either direct or metastatic spread of the tumor; the peripancreatic lymph glands were of normal size and showed no gross evidence of tumor.

Microscopic sections of the pancreas revealed many areas in which pancreatic parenchyma had been completely replaced by fibrocollagenous scar tissue, with only some pancreatic ducts remaining. (Fig. 1.) Other areas showed replacement of parenchyma by tumor in which an arrangement of anastomotic cords resembled that seen in normal islets. (Figs. 2 and 3.) Gomori stains of such areas, as well as of metastatic sites to be described, showed foci with numerous fine granules exhibiting a staining affinity typical of beta cells. (Fig. 4.) In still other areas of pancreas the tumor consisted of small ovoid or spindle cells without characteristic anatomic arrangement. In the liver almost all of the tumor was of the undifferentiated small ovoid or spindle cell type, and was similar to that seen on needle biopsy of the liver during the patient's hospitalization. (Fig. 5.) However, on examination at high magnification, foci of tumor at the junction with normal liver parenchyma revealed vestiges of a cord-like arrangement. (Fig. 6.)

COMMENTS

The phenomenon of an islet cell carcinoma metastasizing as a spindle cell tumor is illustrated in this case. There is no question, after histologic examination and beta cell stains, that the tumor was of islet cell origin. The findings lend credence to the hypothesis of Skillern et al. [*23*] that fibrosarcomas associated with hypoglycemia may really be examples of anaplastic islet cell tumors. However, the line of evidence is far from complete. More cases of extrapancreatic

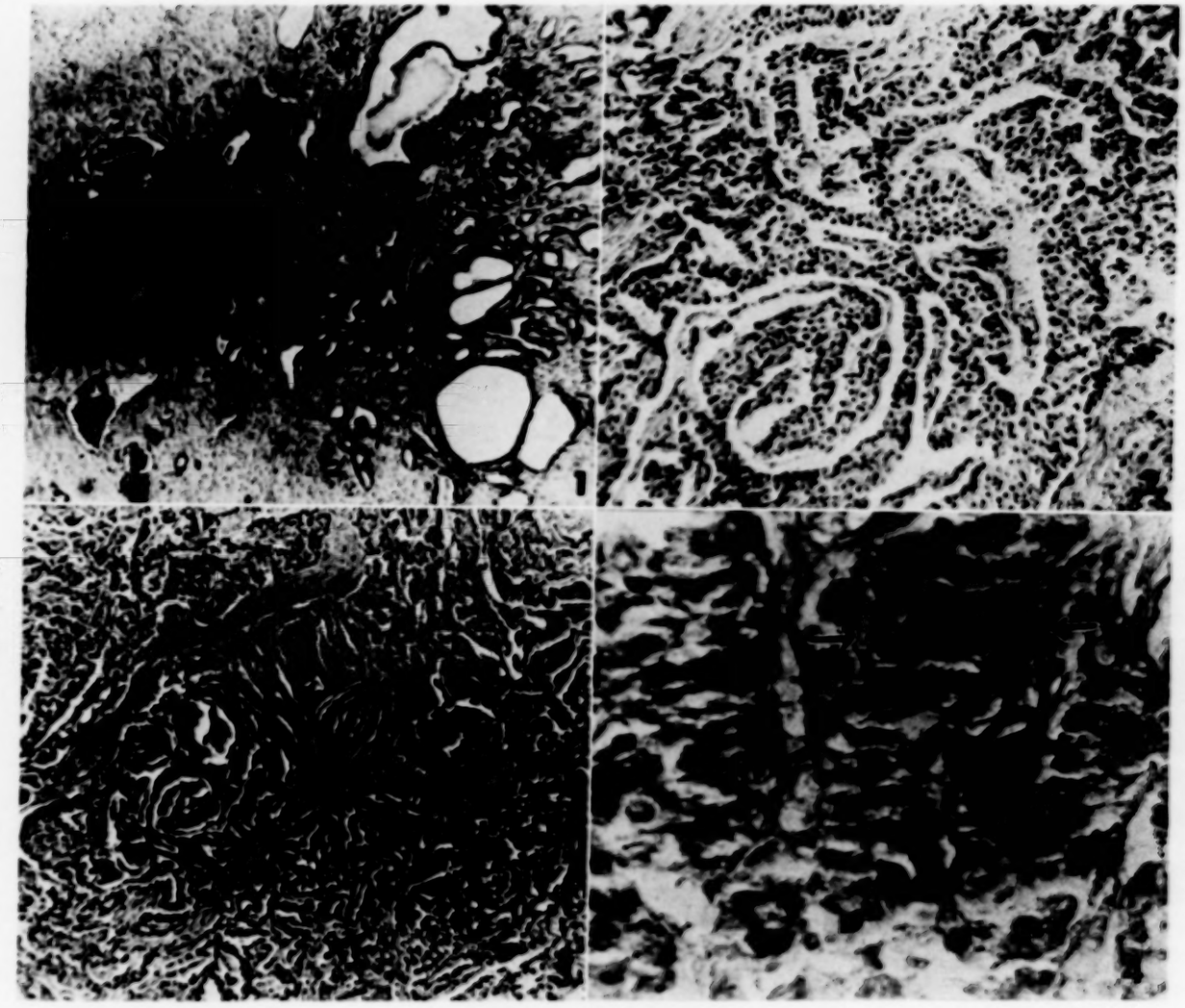

FIG. 1. Pancreas not involved by tumor. Section shows large areas of the pancreas replaced by fibrocollagenous tissue. Only ducts, some of which show cystic dilatation, remain of the parenchyma. Hematoxylin and eosin stain, original magnification × 50.

FIG. 2. Pancreatic tumor. Section shows anastomosing cords of tumor cells in configuration resembling the arrangement of cells of the islets of Langerhans. Hematoxylin and eosin stain, original magnification × 250.

FIG. 3. Pancreatic tumor. Section shows a larger area with numerous nodules showing anastomosing cords of well differentiated islet cell tumor. Hematoxylin and eosin, original magnification × 100.

FIG. 4. Pancreatic tumor. Section shows tumor cells containing beta granules (arrows). Gomori stain, original magnification × 1,000.

tumors associated with hypoglycemia must be assayed for insulin and stained for beta granules. We sorely regret not having performed the former procedure on the anaplastic metastases in this case. Meticulous examination of the pancreas is necessary to uncover possible tiny islet cell tumors giving rise to bulky spindle cell metastases. One cannot resist drawing a parallel between this situation and the well accepted concept of a small unobtrusive carcinoma in the thyroid gland giving rise to a large metastatic "lateral aberrant thyroid."

The possibility also exists that spindle cell tumors which cause hypoglycemia arise from an ectopic pancreas. In 1941 Ballinger [*26*] first reported a case of hypoglycemia from an aberrant islet cell carcinoma, which originated in the liver and metastasized widely. However, the tumor and its metastases all had a typical islet cell appearance. Barbosa, Dockerty and Waugh

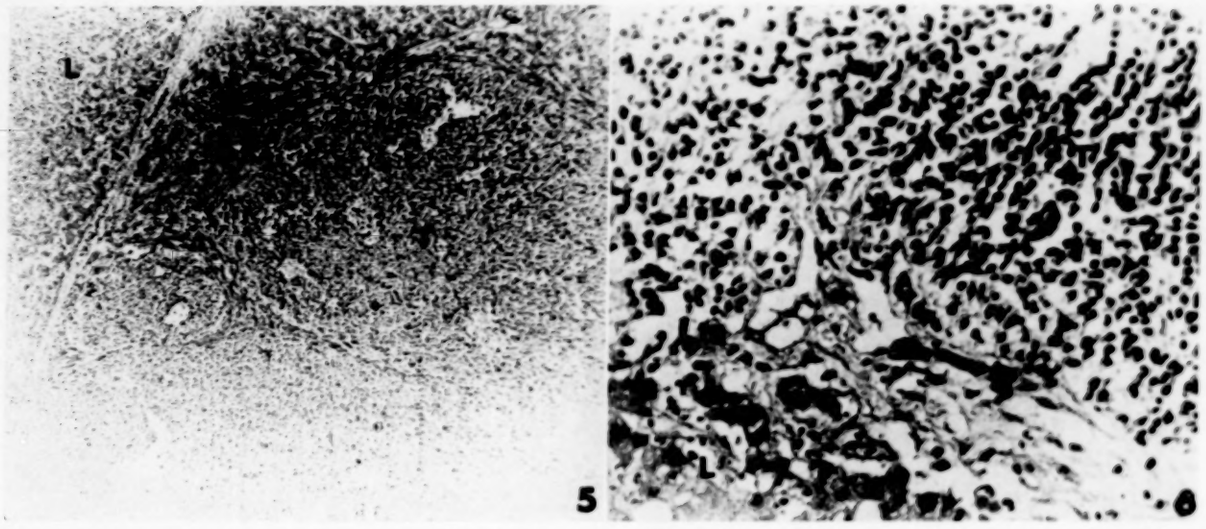

FIG. 5. Hepatic metastases. Section shows nodules of tumor composed of compactly arranged spindle cells (T) adjacent to liver tissue (L). Hematoxylin and eosin, original magnification × 50.

FIG. 6. Hepatic metastasis. Section shows junction of liver tissue and tumor. Arrow indicates an area in which tumor cells are arranged in cords in contrast to the undifferentiated pattern of the remainder of the metastasis, thus indicating a transition from differentiated epithelium to undifferentiated spindle cells. Hematoxylin and eosin, original magnification × 500.

[*27*] in a review of the literature found only six patients with functional islet cell neoplasm arising from an ectopic pancreas. All were in the upper part of the abdomen and all were small tumors that retained their islet cell character. Thus there is no support, as yet, for an ectopic pancreas as the origin of spindle cell tumors.

Other theories concerning the mechanism of hypoglycemia in these tumors are deserving of at least passing comment. Sellman et al. [*21*], after considering various possibilities, concluded that the hypoglycemia in their patient was a result of excessive glucose consumption by the spindle cell tumor. They cited a high tumor level of glycogen and amino acids as support. It is noteworthy that glycogen assay of the liver metastases in our patient yielded low values.* Moreover, a low blood sugar is not characteristic of malignant growths in general. In fact, Woodward and Fry [*28*] found that cancer patients have an average fasting blood sugar level 20 mg. per cent higher than that of normal subjects. Furthermore, the histologic appearance of these hypoglycemia-inducing tumors does not suggest that they are sapping the blood of its glucose to store large quantities of glycogen that cannot be released.

* We are indebted to Dr. Lillian Recant of Washington University, School of Medicine, for these glycogen assays.

Silvis and Simon [*22*] discuss the likelihood that pressure by these tumors on autonomic neuroreceptors may alter the metabolism of the liver in the direction of hypoglycemia. They cite the work of Evans et al. [*29*] who showed that disruption of sympathetic nervous impulses to the liver leads to hypoglycemia in the cat. Seckel [*20*] postulates, in his case report, that a fibroma of the right lobe of the liver pressed on the right splanchnic nerves and celiac ganglion, blocking sympathetic impulses to the liver so that glycogen could not be mobilized. It is hard to imagine how these spindle cell tumors could operate to cause hypoglycemia via a neurogenic mechanism in man when they have been found in such diverse anatomic sites. Even granting such a possibility, why then do not equally bulky tumors in similar sites, but of different histologic types, or tumors with demonstrable perineural invasion, have the same physiologic effect? Rossman [*18*], in a variation on the neurogenic theme, suggested that only tumors arising from the sympathetic nervous system can produce hypoglycemia; he has reported such a case arising from the thoracic sympathetic trunk.

In addition to insulin production, other secretory theories have also been proffered. Scholz et al. [*19*] mentioned Mirsky's work [*30*] and suggests that spindle cell tumors may secrete an

insulinase inhibitor. Nevius and Friedman [*15*] stress the resemblance to another secretory tumor, ovarian thecoma. Their provocative hypothesis holds that these tumors arise from coelomic mesothelium and its underlying mesenchyme, the same tissue which is the origin of the steroid-producing adrenal cortex and gonads. Hence, there would be an ontogenic basis for the production by these tumors of a steroid substance which alters carbohydrate metabolism. In general, however, steroids tend to raise rather than to lower blood sugar.

SUMMARY

A patient with a functional islet cell tumor metastasizing as a spindle cell tumor is described.

The implications of this metaplastic potentiality as they relate to the enigma of extrapancreatic "fibrosarcomas" are discussed. The latter tumors may well represent altered islet cell carcinomas. Alternate theories of how spindle cell tumors may induce hypoglycemia are mentioned.

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Kala-Azar*

A Report of Two Patients Successfully Treated with 2-Hydroxystilbamidine

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Of the infectious diseases, kala-azar provokes one of the most profound reticuloendothelial responses, as manifested by reticuloendothelial hyperplasia and increased levels of serum gammaglobulin (the euglobulin of the earlier literature [*1–5*]). The increased and probably altered [*4,6*] gamma globulin is the diagnostic basis for the several serum flocculation and turbidity tests, i.e., cephalin flocculation, formol gel tests, and thymol turbidity, although diminution of albumin has been shown to be a factor in the cephalin flocculation test [*6*].

We have recently had an opportunity to study and treat two American servicemen with kala-azar. These two patients are reported on in order to call attention to the continuing occurrence of the disease in Americans exposed to it in endemic areas, to review the clinical picture, and to cite our experience with 2-hydroxystilbamidine‡ in treatment of the disease.

CASE REPORTS

Case 1. A twenty-five year-old white Navy man was admitted to the USAF Hospital, Wiesbaden, with chills and fever of six weeks' duration. He had been stationed in Asmara, Eritrea, and was first seen on September 30, 1958, at the USAF Medical Facility in Asmara with a complaint of chills, fever and sweats occurring episodically for one month. He had also noted anorexia (minimal) and a tendency to fatigue. Chills and fever were said to have been associated with the passage of very dark urine. The patient had been in malarial areas of Western Eritrea prior to the time of his illness and stated that he had taken chloroquin in the prescribed manner before going into the malarial areas. Physical examination at the time of initial visit was non-contributory. A tentative diagnosis of malaria was made, although the patient was afebrile at that time and a malaria smear was negative. The patient was treated with primaquine.

Three days after the initial visit the patient experienced two more episodes of chills and fever associated with the passage of dark urine. Physical examination at that time revealed the presence of a moderately tender liver, the edge of which was palpated at the right costal margin. Although the spleen was not palpated, there was marked tenderness in the left upper quadrant of the abdomen. A diagnosis of hepatitis was made and the patient was placed on quarters.

Six days after the patient's initial visit, he was admitted to the hospital as a result of a blood count which revealed the following: hemoglobin 11.5 gm. per cent; white blood cells 5,300 per cu. mm. with 54 per cent polymorphonuclears and 4 per cent lymphocytes; hematocrit 36 per cent, reticulocyte count 6 per 1,000 red cells. On the second day of his hospitalization he experienced two episodes of chills and fever, the temperature spiking to 101° and 103.8°F. intermittently. A urine specimen was examined at this time and was non-contributory. A malaria smear again was negative. At this time the white blood cell count was 5,100 per cu. mm. with 33 per cent polymorphonuclears and 63 per cent lymphocytes. No atypical forms were noted. The hemoglobin and reticulocyte concentrations remained unchanged. The serum bilirubin at this time was 0.5 mg. per cent. Repeated physical examination is said to have revealed "discrete tender epitrochlear and popliteal lymph nodes." A presumptive diagnosis of infectious mononucleosis associated with hemolytic anemia was made at this time and the patient was evacuated to the USAF Hospital, Wiesbaden; admission took place on October 13, 1958.

Physical examination at the time of admission revealed a somewhat pale, well developed white man who appeared chronically ill. There was apparent moderate

‡ 2-Hydroxystilbamidine will hereafter be referred to as hydroxystilbamidine.

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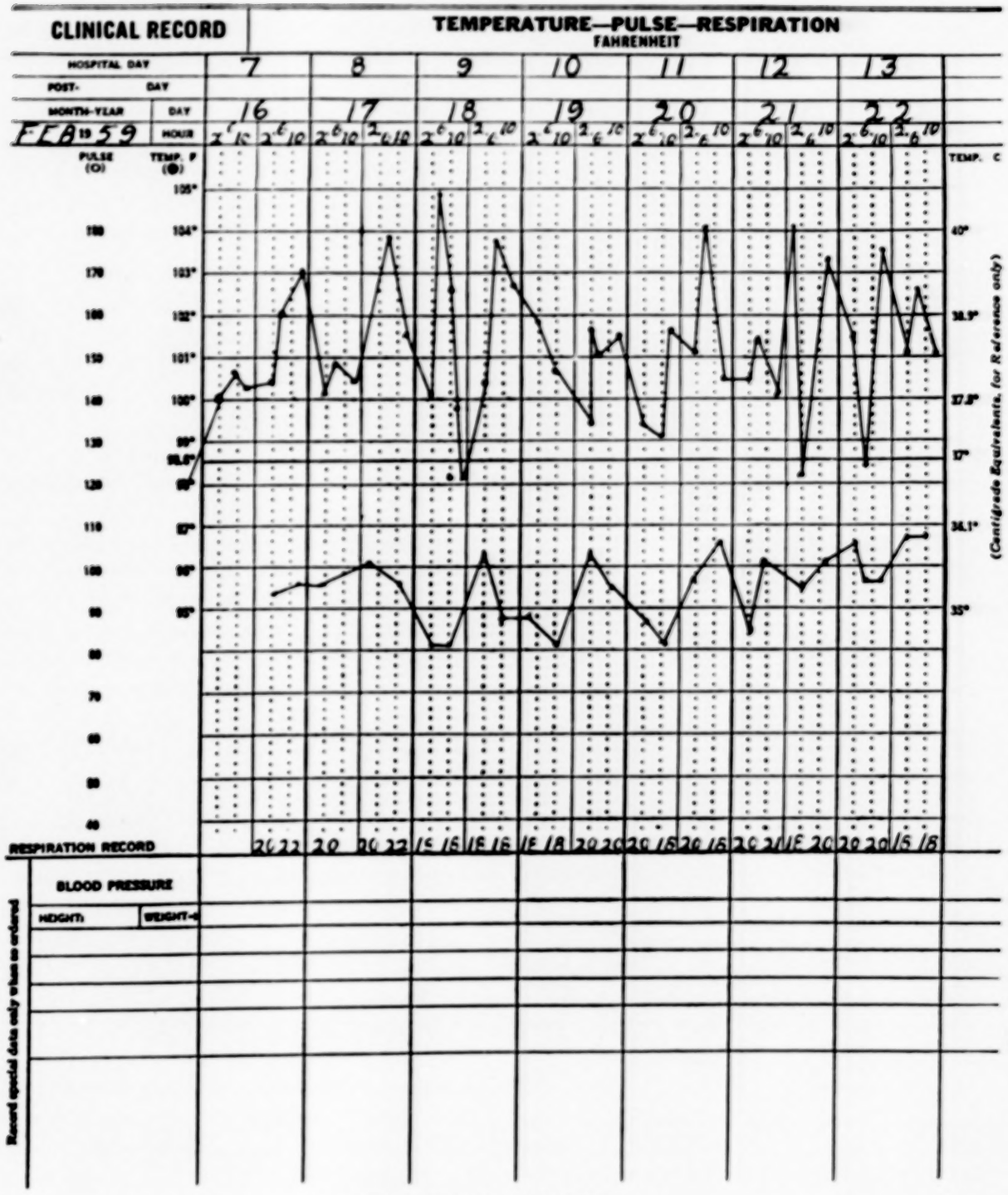

FIG. 1. Clinical record of Case 1.

recent weight loss. Examination of the head, neck, chest, heart was non-contributory. Examination of the abdomen revealed a non-distended, soft abdomen with definite fist percussion tenderness over the right inferior anterior thoracic cage, and a markedly tender liver edge could be palpated with deep inspiration. The upper border of liver dullness was percussed at the fifth intercostal space. The splenic tip was palpated by one observer and was non-tender. Physical examination otherwise revealed no

abnormalities; there was no icterus, local or general adenopathy. Initial blood count revealed: a white count of 4,500 per cu. mm. with 42 per cent neutrophils, 67 per cent lymphocytes, 1 per cent monocytes. The hemoglobin was 11.9 gm. per cent, hematocrit 38 per cent, corrected erythrocyte sedimentation rate 24 mm. The urinalysis was negative. Results of blood serological tests were negative. The morphology of the red blood cell was normal. The reticulocyte count was 0.5 per cent. Coombs' test, direct and indirect, had negative results. A two-hour urobilinogen was 0.22 mg. (normal). The heterophil titer was 1:7. Five peripheral blood smears were negative for malaria. Febrile agglutinins including typhosa "O," typhosa "H," paratyphi, S. schottmuelleri, and Brucella abortus were all within normal limits. The serum bilirubin was 0.54 mg. per cent, cholesterol 130 mg. per cent, alkaline phosphatase 4.8 Bodansky units, thymol turbidity 30 units, cephalin flocculation 3 plus in forty-eight hours, total protein 6.8 gm. per cent with 3.5 gm. albumin and 3.3 gm. globulin. Electrophoretic pattern revealed 34.6 per cent gamma globulin or 2.4 gm. per cent (normal average 17.8 per cent or 1 gm.). The prothrombin time was eighteen seconds with control of thirteen seconds. The bleeding time was normal. The platelet count was 300,000 per cu. mm. (Prothrombin time following intravenous vitamin K therapy for three days was fifteen seconds with a control of thirteen seconds.) A repeat white blood cell count fifteen days after admission showed 4,500 cells per cu. mm. In the bromsulfalein test there was 21 per cent dye retention in forty-five minutes. The serum iron was 0.21 mg. per cent. The blood urea nitrogen was 12 mg. per cent. Three stool examinations for ova and parasites had negative results. Three blood cultures were negative. Results of skin tests for purified protein derivative No. 1 and 2, histoplasmin, coccidiodin, blastomycin and mixed bacterial vaccine were negative. The patient's blood type was B positive; type A red cells agglutinated normally. Leukocyte agglutinins could not be demonstrated. Two electrocardiograms were within normal limits. A bone marrow differential count revealed some hyperplasia of the red cell series, the myeloid-erythroid ratio being 2.7:1. Roentgenograms of the chest revealed no abnormalities. Supine and erect x-ray films of the abdomen on October 28 revealed the spleen to be enlarged about three times the normal size.

The hospital course prior to initiation of specific therapy was characterized by an intermittent doubly spiking fever diurnally, the peaks reaching as high as 105°F. (See Fig. 1.) The patient, however, did not appear acutely ill even at the time of the paroxysm of fever. Because of the type of febrile clinical picture, the fact that the patient was formerly in East Africa, his inordinately good appearance, splenomegaly, low white count and marked hypergamma-globulinemia, a diagnosis of visceral leishmaniasis was entertained. A biopsy specimen of liver was obtained and typical Leishmania donovani bodies were demonstrated within the Kupffer cells. Results of a bone marrow examination for Leishmania donovani bodies were negative. A culture of the bone marrow aspirate also was negative for Leishmania organisms.

On November 12, one month after admission, the patient was started on daily treatment with hydroxystilbamidine, 225 mg. in 200 cc. of 5 per cent dextrose in water intravenously. This was continued until December 15. The patient became afebrile on November 19, seven days after initiation of therapy. There was a gradual reduction in the size of the spleen and on November 28 the spleen was no longer palpable. A repeat biopsy specimen of the liver was obtained one month after initiation of treatment to confirm that the infecting organism was no longer present. The patient's hemoglobin and white blood cell count began to rise within a week after initiation of therapy. After treatment for four weeks the hemoglobin had risen to 11.9 gm. per cent and the white count was 12,350 per cu. mm. The serum total protein had risen to 8.3 gm. per cent; the albumin had risen from 2.7 to 2.9 gm. per cent; the serum globulin, however, had also risen from 5.2 to 5.4 gm. per cent, the gamma fraction increasing from 42.8 per cent to 43.4 per cent. (See Chart 1.) At this time the patient was asymptomatic and continued to be asymptomatic until the time of his discharge on December 15, 1958, thirty-five days after initiation of therapy. At the time of his discharge the patient's hemoglobin was 13.9 gm. per cent, white blood cells 6,700 per cu. mm., serum total protein 7.7 gm. per cent, albumin 3, globulin 4.4, gammaglobulin 2.9 gm. per cent. Six weeks following discharge the patient remained asymptomatic.

Case II. This thirty-six year old Caucasian man was admitted to the USAF Hospital, Wiesbaden, for evaluation of fever of unknown cause; the patient was admitted as a transfer from his base hospital in Spain. The patient's illness began three weeks prior to the time of admission with the sudden occurrence of daily fever, shaking chills, and sweats. One week after the onset of his illness the patient was admitted to his base hospital with complaints of dull anterior chest pain, episodic pleuritis left chest pain, and a nonproductive cough. He had become somewhat anorectic and had lost 11 pounds. The patient had been stationed in Madrid, Spain, for eighteen months prior to hospital admission. He had been outside of the Madrid area twice. He had gone to Casablanca, Morocco, one year prior to his admission, during which time he spent two hours ashore and the remainder of two days in the harbor aboard his ship. He had been to Barcelona for one day five months prior to the time of his admission; he did not recall having been bitten by insects. He had served in the South Pacific in 1945 and had also served in Puerto Rico and in the United States since that time. Physical

FEVER TYPE		I. S.	I. S.	I. S.	I. S.	I. S.	___	___	___							
HEIGHT		100-1	102-4	102-3	102-3	102-3	NORMAL	NORMAL	NORMAL							
NUMBER OF ELEVATION PER 24 HOURS		1	2	2	2	___	___	___	___							
LIVER SIZE		6 cm				6 cm.	4 cm	2 cm	___	___	___					
SPLEEN SIZE		ILLIAC CREST				ILLIAC CREST	10 cm	2 cm	___	___	___					
HEMATOCRIT & HB		38 11.4		34 10.4		26 8.1	32 10.3	37 11.6	37 11.9	41 12.9	43 13.9					
W. B. C.		4,500		4,500		2,400	3,400	4,650	12,350	13,500	6,700					
TOTAL PROTEIN	NORMAL%	7.4	6.8			7.9			8.3		7.7		8.1		7.7	
ALBUMIN	52.3	3.8	43.6 3.3			34.4 2.7			34.6 2.9		39.1 3.3		47.7 3.9		54.6 4.2	
GLOBULIN	47.7	3.6	56.4 3.5			65.6 5.2			65.4 5.4		60.9 4.4		52.3 4.2		45.4 3.5	
ALPHA$_1$	4.4		3.7 0.2			7.1 0.5			3.6 0.3		5.4 0.4		3.3 0.3		2.5 0.2	
ALPHA$_2$	12.0		11.8 0.7			4.8 0.4			7.9 0.6		8.0 0.6		5.6 0.4		7.3 0.6	
BETA	13.5		7.4 0.5			10.9 0.9			10.5 0.9		10.4 0.8		14.3 1.2		11.0 0.8	
GAMMA	17.8		33.5 2.4			42.8 3.4			43.4 3.6		37.1 2.8		29.1 2.3		24.6 1.9	
THYMOL T		24	30			41	42		43	48			22		23	
CEPH FLOC.		3,4					2,3			3,3	3,3					
PROTHROMBIN		13-18								13-16						
B. S. P.		21%					5%	5.5%								
WEEK AFTER ADMISSION		1	2	3	4	5	6	7	8	9	10	11	12	13	16	

HYDROXY STILBAMIDINE STARTED ON 29th HOSPITAL DAY.

LEISHMANIA D. DEMONSTRATED.

LEISHMANIA D. NOT DEMONSTRATED.

HYDROXY STILBAMIDINE DISCONTINUED ON 62nd HOSPITAL DAY.

DISCHARGED

CHART 1. Case 1. I. S. = intermittent spiking. The bromsulphalein (B.S.P.) per cent in forty-five minutes.

FEVER TYPE		I. S.	I. S.	I. S.									
HEIGHT		104–102	102–104	100–102	98.6-99.8	99.8	99	98.6	98.6	98.6			
NUMBER OF ELEVATION PER 24 HOURS.		2	2	2	1	1							
LIVER SIZE		13 cm.	13 cm.	13 cm.	10 cm.	8 cm	6 cm.	6 cm.	6 cm.	4 cm.			
SPLEEN SIZE		11 cm.	11 cm.	11 cm.	8 cm.	6 cm.	4 cm.	4-5 cm.	4 cm.	3 cm.			
HEMATOCRIT & HB		28 9.4	26 8.5	30 9.6	35 11.4	37 12.4	39 12.2	40 12.9	41 13.7	44 14.4			
W. B. C.		5,900	1,650	3,100	7,300	12,300	6,300	6,100	8,000	5,800			
TOTAL PROTEIN	*NORMAL %*	5.8	6.1		6.5	6.8	6.0			5.8			
ALBUMIN	52.3	41.0 | 2.4	32.4 | 2.0		37.1 | 2.4	50.6 | 3.4	54.8 | 3.3			4.1			
GLOBULIN	47.7	59.0 | 3.4	67.6 | 4.1		62.9 | 4.1	49.4 | 3.4	45.2 | 2.7			1.7			
$ALPHA_1$	4.4	10.7 | 0.6	8.9 | 0.5		6.6 | 0.4	3.8 | 0.3	3.2 | 0.2						
$ALPHA_2$	12.0	10.2 | 0.6	13.0 | 0.8		7.2 | 0.5	8.0 | 0.6	11.4 | 0.7						
BETA	13.5	14.1 | 0.8	9.1 | 0.6		11.7 | 0.8	10.9 | 0.7	11.5 | 0.7						
GAMMA	17.8	24.5 | 1.4	36.6 | 2.2		37.4 | 2.4	26.7 | 1.8	19.1 | 1.1						
THYMOL T		9 UNITS	———	16 UNITS	———	18 UNITS	4 UNITS			10 UNITS			
CEPH FLOC.		3,3	———	3,3	3,4	3,3	1,2			–,1			
PROTHROMBIN		20 – 13	18 – 13	15 – 13	17 – 13	16 – 13	17 – 13			13 — 13			
B. S. P.		10%	———	———	———	———	5%			———			
WEEK AFTER ADMISSION		1	2	3	4	5	6	7	8	9			

LEISHMANIA D. DEMONSTRATED. (week 2)

HYDROXY STILBAMIDINE STARTED ON 10th HOSPITAL DAY. (week 2)

LEISHMANIA D. NOT DEMONSTRATED. (week 5)

HYDROXY STILBAMIDINE DISCONTINUED ON 46th HOSPITAL DAY. (week 7)

CHART 2. Case II. B.S.P. in forty-five minutes.

examination at that time is said to have revealed a temperature of 103.6°F., pulse 100, "two finger-breadths" hepatomegaly and "minimal" splenomegaly. Laboratory studies at that time revealed a white blood cell count of 2,300 per cu. mm. with 48 per cent neutrophils and 52 per cent lymphocytes. The hemoglobin was 9.4 gm. per cent.

The patient's hospital course in Spain was characterized by a double-spiking fever diurnally in the range of 104 to 105°F. Because blood cultures revealed gram-positive rods which were thought to be typhoid organisms, the patient was started on chloromycetin and penicillin therapy but his clinical course remained unchanged. He was given transfusions of whole blood on three occasions because of a gradually decreasing hematocrit.

Physical examination at the time of admission to the USAF Hospital, Wiesbaden, revealed a temperature of 103°F., pulse 110, respiration 18. The patient was a thin white man, pale, acutely and chronically ill. There was minimal enlargement of the axillary lymph nodes. Funduscopic examination revealed two white areas, one-half disc diameter, in the superior medial retinal quadrant of the right eye and a similar area in the left eye. These were thought to be cytoid bodies. Examination of the chest and heart was non-contributory. The abdomen was moderately distended and revealed a prominent venous pattern without radiation from the umbilicus. The liver was palpated 13 cm. below the right costal margin in the mid-clavicular line and was not tender. The remainder of the physical examination revealed no abnormalities.

Laboratory studies on admission were: white blood cells 5,900 per cu. mm. with 65 per cent neutrophils, 34 per cent lymphocytes, 1 per cent monocytes. The erythrocyte sedimentation rate was 17 mm., hemoglobin 9.4 gm. per cent, hematocrit 28 per cent, serum total protein 5.8 gm. per cent, albumin 2.4 gm. per cent, globulin 3.4 gm. per cent, alkaline phosphatase 11.4 Bodansky units. The cephalin-flocculation test was 3 plus in forty-eight hours, the thymol turbidity 9 units. Bromsulphalein retention was 10 per cent in forty-five minutes. The serum bilirubin was 0.56 mg. per cent. The reticulocyte count was 0.5 per cent. Serum transaminase, lupus erythematosus preparation, tests for typhosa "O," typhosa "H," parathyphi, S. schottmuelleri and Brucella abortus were all within normal limits. Serum protein electrophoresis revealed a gammaglobulin of 1.4 gm. per cent, approximately one and a half times normal.

The hospital course prior to the time of diagnosis and specific treatment was characterized by a continuance of double-spiking fever diurnally, the peaks being 103 to 104°F. and a progressive diminution of the white blood cell count, which was 1,650 per cu. mm. on the tenth hospital day. The spleen was palpated on the seventh hospital day, the edge being 4 cm. beneath the left costal margin. On the eleventh hospital day the diagnosis of visceral leishmaniasis was established by the demonstration of Leishmania donovani organisms in the Kupffer cells of the liver, by punch biopsy of the liver. On the eleventh hospital day the patient was started on hydroxystilbamidine 225 mg. per day intravenously. Thereafter the temperature decreased gradually to normal after ten days. There was a concomitant decrease in the size of the liver and spleen, and gradual disappearance of the patchy white areas in the fundi. The patient's hemoglobin and white blood cell count began rising within a week after institution of therapy, and three weeks after therapy both had become essentially normal. During this three week period the patient was given 500 cc. of whole blood. A repeat biopsy of the liver was performed on the thirty-second hospital day, twenty-one days after institution of specific therapy. No Leishmania donovani were demonstrated. There was some increase in the amount of bile pigment noted in the liver cells and some residual hyperplasia of the Kupffer cells. Hydroxystilbamidine therapy was discontinued on the forty-sixth hospital day, a total dose of 7,805 mg. having been given. The patient's only complaints were occasional muscle aches, usually occurring at night at rest, predominantly in the legs. The liver and spleen were still moderately enlarged, the liver being palpated 3 cm. below the right costal margin, the splenic tip 2 cm. beneath the left costal margin. The patient was observed for approximately four weeks after discontinuance of specific therapy. During this time the liver and spleen continued to diminish in size until no longer palpable. The serum protein, which had previously shown a further increase in the gammaglobulin fraction two weeks after the institution of treatment, gradually reverted toward normal. (See Chart 2.) The patient was completely asymptomatic at the time of his discharge on the sixty-ninth hospital day.

COMMENTS

Kala-azar is an infectious tropical disease that is most common in Central and East Africa, East India, China, Burma, and the coastal area bordering the Mediterranean Sea. It is also endemic in South America, but patients with overt clinical manifestations are not common. Leishmania donovani is the infecting organism and its vector is the phlebotomus sand fly. In most areas man serves as the principal reservoir of infection, but in the Mediterranean area the dog is thought to be a major reservoir. The disease is most common in children, and in the Mediterranean type it is uncommon in adults. Newcomers to endemic areas appear to be particularly susceptible to this disease. A rural location, a ground level habitant, and any condition

enhancing contact with the sand fly increase the likelihood of infection in endemic areas. From this it is plain that American servicemen quartered in temporary housing in rural areas and taking part in training exercises in these areas would be especially susceptible to infection.

According to Shattuck [7], the usual incubation period is two to four months. There are, however, reports of patients in whom incubation periods ranged from "under ten days" [8] to thirty-four months [9]. The disease may be abrupt or insidious in its onset. It commonly presents like and is misdiagnosed as malaria since double and triple diurnal, rapidly remitting fever spikes (103° to 104°F.) are apt to dominate the clinical picture. More commonly the onset is gradual. As in malaria also, there are usually associated chills and sweats; unlike malaria, however, debilitation does not usually occur, at least early in the course of the disease. Indeed, one of the most striking characteristics of the disease is the disparity between the subjective feeling and clinical appearance of the patient, and the objective severity of the disease. In both of our patients the observation was repeatedly made that, while undergoing a paroxysm of fever, the patient had no particular complaints and did not appear uncomfortable. The appetite is usually not markedly impaired but there tends to be a steady loss of weight.

With chronicity of the disease, the patient becomes more or less emaciated. The skin is generally pale but in many cases is said to become a peculiar dusky grey color, which is the basis for the native name, kala-azar, "the black disease." According to Manson [8], this color is best seen on the feet, hands and abdomen in Europeans, although it is very difficult to distinguish in dark-skinned natives. According to Napier [10], pigmentation may be markedly intensified on the forearms and temples in dark-skinned people, but not in white-skinned people. In neither of our patients was there a change in the color of the skin, and in none of the thirty American servicemen with kala-azar reported on by Most and Lavietes [4] was there a change in the color of the skin.

Generalized lymphadenitis is common. In soldiers who contracted kala-azar in Sicily and North Africa in 1943, several showed only lymphadenitis, the cervical area being most prominently involved [8]. Examination of the chest and heart is usually non-contributory. Splenic enlargement is present from the start and commonly becomes extreme. Napier [10] describes the spleen as having soft doughy consistency and states that unlike malaria it does not become hard with chronicity. In one of our patients a spleen extending to the iliac crest was missed initially because of its soft spongy quality. The liver is frequently somewhat enlarged. It will be noted that in one of our patients (Case II) the liver was larger than the spleen. Neither the liver nor the spleen is especially tender. Edema of the lower legs and feet is a common finding and usually reflects lowered serum albumin.

Anemia and leukopenia are invariable in well established cases. The anemia is of no consistent type. Reticulocytes are usually increased. According to Manson [8], the leukocytes are reduced to below 3,000 per cu. mm. in 95 per cent of patients, below 2,000 in 73 per cent, and below 1,000 in 42 per cent. The tendency towards agranulocytosis accounts for the increased susceptibility to secondary infections. There is usually a relative lymphocytosis. The platelets are moderately decreased. Sen Gupta [11] believes that the leukopenia, anemia and thrombocytopenia are the result of hypersplenism. The reported increase in the red blood cell count in response to epinephrine (injected) is consistent with this idea [9].

Characteristically there is a diminution of the serum albumin and an increase of serum globulin. The globulin elevation is in large part due to elevation of the gamma fraction (euglobulin). The gammaglobulin elevation tends to increase with chronicity and levels of 6 gm. are not uncommon. (One gm. is the usual average normal.) The cause of the gammaglobulin alteration and elevation is not well understood. Because of the common association of hypergammaglobulinemia and diseases associated with disturbances of the reticuloendothelial system, a cause-effect relationship is thought to exist. Tuberculosis, lymphogranuloma venereum and sarcoidosis are such diseases. There is good evidence that the plasma cell is the principal site of origin of gammaglobulin [12,13]. Proliferative disorders of the reticuloendothelial system associated with hyperglobulinemia and hypergammaglobulinemia in particular, such as plasma cell myeloma, chronic lymphocytic leukemia and Waldenström's macroglobulinemia, are almost invariably associated with plasmacytosis of the bone marrow [14]. Conversely, plasmacytosis of the

bone marrow from any cause is usually associated with hyperglobulinemia [*15*]. Reticuloendothelial proliferation would then appear to effect hyperglobulinemia by way of a plasmacytotic mechanism.

The morphologic pathology of kala-azar is consistent with this idea. The basic pathologic disorder of kala-azar is phagocytosis of the infecting Leishmania donovani and hyperplasia of the reticuloendothelial system. This is best seen in the spleen, liver and bone marrow. Microscopically, the spleen shows masses of parasites packed in numerous large mononuclear phagocytes; plasmacytes and lymphocytes are also quite numerous. The reticuloendothelial cells of the liver, the Kupffer cells, similarly contain many parasites. Examination of the bone marrow may reveal numerous parasite-containing phagocytes, occasional parasite-containing myelocytes and polymorphonuclears, and increased numbers of plasma cells. The phagocytized parasites are known as Leishmania donovani bodies. Identification of these bodies, of course, establishes the diagnosis. The spleen most frequently yields Leishmania donovani bodies, the liver and bone marrow being next in frequency.

Until 1939, antimony compounds constituted the only consistently effective treatment for kala-azar. At this time stilbamidine was introduced and used successfully for the treatment of kala-azar [*16*], even in patients who had been refractory to antimony treatment. Because of serious neurologic and renal complications, the drug has been used with considerable reluctance. In 1948 a new stilbamidine compound, 2-hydroxystilbamidine was first used successfully by Sen Gupta [*17*] in the treatment of kala-azar. Since that time Sen Gupta has had marked success with hydroxystilbamidine in a large series of patients, with virtual freedom from complications of therapy [*18*]. Of particular importance is the fact that there has been no report of the curious trigeminal neuritis associated so frequently with the use of stilbamidine. Moreover stilbamidine has been used successfully in cases of the Sudanese variety of kala-azar, a type notoriously resistant to antimony therapy.

Our first patient, who may be judged to have had the Sudanese variety of kala-azar because of his location in Eritrea, was therefore treated with hydroxystilbamidine. The results were altogether satisfactory. Because of our success in the first patient, hydroxystilbamidine was also used in the second patient, and with equal success.

It is of note that the elevated gammaglobulin in Case 1 had not diminished when eradication of the infecting organisms had been demonstrated by biopsy. A continued rise in serum globulin for some time after institution of treatment and apparent successful clinical response can be noted in Stone's case [*9*] and in three patients reported on by Most and Lavietes [*4*]. Sen Gupta [*11*] believes that the continued presence of blood congestion in the spleen serves as a continuing stimulant to reticuloendothelial activity and continued hypersplenism. If there is such a continued reticuloendothelial stimulation, this could explain a continuing hyperglobulinemic response.

SUMMARY

Two cases of kala-azar are presented herein. The clinical picture is reviewed and our experience with 2-hydroxystilbamidine in the treatment of kala-azar cited.

The serum gammaglobulin elevation did not diminish concomitantly with successful clinical response and in one case remained undiminished at a time when leishmania organisms could no longer be demonstrated.

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Increased Insulin-Like Activity of the Serum in a Patient with Spontaneous Hypoglycemia Associated with a Retroperitoneal Fibrosarcoma*

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THE occurrence of spontaneous hypoglycemia in patients with non-pancreatic tumors has been described with increasing frequency during the past few years. In their survey of the literature on this subject Howard and Davis [*1*] were able to find fourteen cases, of which ten had been reported since 1954. Since the publication of their article, three more cases of spontaneous hypoglycemia associated with tumors have been described [*2,3,4*].

To the best of our knowledge, only August and Hiatt [*5*] have reported successful extraction of insulin activity from the tumor itself. However, their assay of plasma insulin-like activity in the patient before removal of the tumor mass was within normal limits [*5*].

Admission to the University of Arkansas Medical Center Hospital of a patient with spontaneous hypoglycemia associated with a retroperitoneal fibrosarcoma provided another opportunity to investigate the plasma insulin-like activity in this situation. The paper presented herein reports our finding of increased insulin-like activity in the serum of the patient during the spontaneous hypoglycemic episodes.

CASE REPORT

A thirty-nine year old white woman had noted numerous episodes of non-periodic weakness and nervousness in September 1958. These episodes followed an ill-defined illness with symptoms of fever and anorexia. In December 1958, she experienced episodes of extreme sweating, tremulousness and nervousness, which usually occurred in the early morning and were promptly relieved by the ingestion of food. The episodes increased in frequency and severity, and in January 1959, the patient was admitted to a hospital in a comatose state. At the time of her admission the blood sugar was 28 mg. per 100 ml. The coma was immediately relieved with the administration of intravenous glucose. In February 1959 an exploratory laparotomy was performed and the distal one-third of the pancreas and the spleen were resected. Histologic sections revealed normal islet cells and pancreatic fibrosis. Because of persistence of the hypoglycemic episodes the patient was transferred to the University of Arkansas Medical Center on March 10, 1959.

Physical examination revealed a well developed and nourished woman who was perspiring excessively. The temperature was 101°F. and there was a sinus tachycardia of 102. Signs of a left pleural effusion were noted. There was a transverse scar across the upper part of the abdomen with a sinus draining purulent material at the left lateral margin of the scar.

The blood sugar was 22 mg. per 100 ml. on admission. The serum electrolytes were within normal limits except for a serum potassium of 3.2 mEq. per L. Results of liver function tests and a serum amylase were normal. Adrenocortical function was normal.

The hospital course was characterized by repeated hypoglycemic episodes whenever there was interference with the intravenous administration of glucose. A left subphrenic abscess which required incision and drainage, a femoral thrombophlebitis, and an Aerobacter aerogenes bacteremia complicated the clinical course.

On June 10, 1959, a large retroperitoneal tumor was resected. There was no evidence of liver metastases. There was no attachment to the pancreas. The tumor was a large, gray, lobulated mass which weighed 1,570 gm. Some portions of the tumor were yellow and

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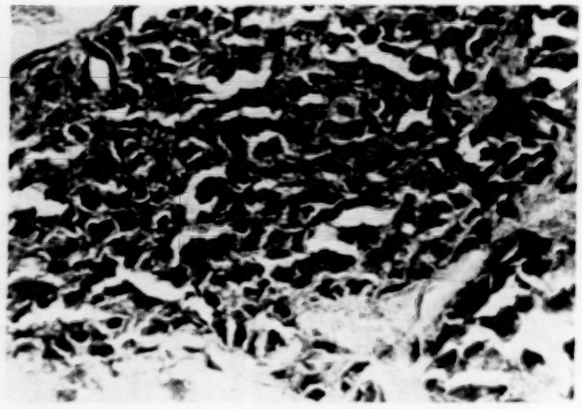

FIG. 1. Section of tissue showing sheet-like stroma consisting of numerous pleomorphic spindle-shaped cells. The nuclei show marked pleomorphism and hyperchromatism.

firm, others were soft, necrotic and hemorrhagic. Microscopic examination of the tumor revealed a sheet-like stroma consisting of numerous pleomorphic spindle-shaped cells. The nuclei showed marked pleomorphism and hyperchromatism. (Fig. 1.) Necrosis and hemorrhage were noted in adjacent areas.

Postoperatively, hyperglycemia and glucosuria were present for eight days. Subsequent blood sugars have been normal and a glucose tolerance test in July 1959, was normal. When the patient was last seen in January 1960, she was asymptomatic and there was no evidence of recurrence of the tumor. A two hour postprandial blood sugar was 84 mg. per 100 ml.

ASSAY FOR SERUM INSULIN-LIKE ACTIVITY

Serum insulin-like activity was assayed on samples prepared from blood drawn from both the patient and normal control subjects in the morning before breakfast. The serums were stored frozen at minus 18°C. until the time of the assay.

Two blood samples were obtained preoperatively, the first on March 12 shortly after her admission to the hospital, the second on June 9 the day before her operation. Two postoperative samples also were obtained, one on June 18, eight days following surgery, and one approximately four months later, on October 20.

The glucose concentration in each serum was measured. Each sample was then diluted 1:1 with Krebs-Ringer bicarbonate buffer [*6*] and the final glucose concentration of each diluted sample was adjusted to a glucose concentration of 2.5 mg. per ml. The term serum from now on will refer to the diluted serum.

Hemidiaphragms from male rats weighing between 100 and 150 gm. who had been previously fasted for sixteen to twenty hours were prepared. Pairs of hemidiaphragms were soaked for approximately 10 minutes in 4 to 5 ml. Krebs-Ringer bicarbonate buffer containing 2.5 mg. per ml. glucose. Each hemidiaphragm was then transferred, with gentle blotting, to a beaker containing 1 ml. of the previously diluted serum. The hemidiaphragms were incubated for one hour at 37°C. in a gas phase of 95 per cent O_2 to 5 per cent CO_2. At the end of the incubation period the hemidiaphragms were weighed on a torsion balance. The initial and final glucose content of each beaker was measured by the method of Somogyi [*7*]. The glucose disappearance from each beaker was calculated in terms of milligrams of glucose utilized per gram tissue wet weight per hour.

In one assay for insulin activity, epididymal fat pads were used. The procedure was as follows: the fat pads were taken from rats weighing between 100 and 150 gm. which had been fasted for sixteen to twenty hours. Each fat pad was carefully dissected out and dropped directly into 1 ml. of serum. The fat pads were incubated for three hours at 37°C. in a gas phase of 95 per cent O_2 to 5 per cent CO_2. The fat pads were weighed and the glucose content of each beaker measured. Glucose uptake was calculated as milligrams of glucose disappearing per gram tissue wet weight per three hours.

The statistical significance of the changes observed were calculated by Fisher's t test.

An increase of the glucose uptake of either the hemidiaphragms or the epididymal fat pads in the presence of the patient's serum over that in the control serum was interpreted as representing increased blood insulin-like activity. No attempt has been made in these studies to assess serum insulin-like activity in terms of units per milliliter because of the large variations in reports of serum insulin activity from one laboratory to another [*8*].

The patient's blood sugar was 70 mg. per 100 ml. shortly after admission to the hospital when she was receiving a constant intravenous infusion of 10 per cent dextrose and 24 mg. per 100 ml. on the day before surgery. Eight days following removal of the tumor her blood glucose level was elevated to 108 mg. per 100 ml. and four months later was 78 mg. per 100 ml.

The glucose uptakes of the diaphragms of the rat and the epididymal fat pads incubated in the

TABLE 1

THE GLUCOSE UPTAKES OF HEMIDIAPHRAGMS OR FAT PADS OF THE RAT INCUBATED IN SERUM FROM A TUMOR-BEARING PATIENT COMPARED TO UPTAKES IN SERUM FROM CONTROL SUBJECTS

Serum	Glucose Uptake† (mg./gm.)	p‡
Assay 1 (Uptake of Diaphragm Tissue per Hour)		
Control	5.32 ± 0.22 (5)	
Control plus insulin*	7.32 ± 0.38 (5)	<0.01
Patient		
Preoperative (3/12/59)	7.25 ± 0.26 (5)	<0.001
Assay 2 (Uptake of Diaphragm Tissue per Hour)		
Control	4.07 ± 0.28 (5)	
Control plus insulin*	5.76 ± 0.26 (5)	<0.01
Patient		
Preoperative (6/9/59)	5.88 ± 0.37 (5)	<0.01
Postoperative (6/18/59)	4.25 ± 0.22 (5)	=0.10
Assay 3 (Uptake of Fat Pad Tissue per Three Hours)		
Control	4.26 ± 0.20 (6)	
Patient		
Preoperative (6/9/59)	5.13 ± 0.22 (6)	<0.05
Postoperative (6/18/59)	4.28 ± 0.33 (6)	=0.10
Postoperative (10/20/59)	3.39 ± 0.36(6)	<0.01

NOTE: For assay 1 the serum was obtained shortly after hospital admission; for assay 2 the serum was obtained before operation and eight days postoperatively; for assay 3 the serum was obtained at the same time as for assay 2 plus an additional postoperative sample.

* Crystalline insulin present at a concentration of 0.1 units/ml.

† Glucose uptake ± the standard error of the mean. The numbers in parentheses indicates the number of pieces of tissue in each group.

‡ p shows the significance of the difference in glucose uptake of each group compared to its own control group.

patient's serum are shown in Table 1. In the first assay using hemidiaphragms, the patient's serum collected March 12 stimulated glucose uptake to a degree comparable to that caused by the addition of 0.1 units per ml. insulin to the control serum.

The second assay, again using hemidiaphragms, was carried out on two serum samples, one collected just before the operation (June 9) and the other eight days postoperatively (June 18). The preoperative sample, which had a glucose level of 24 mg. per cent, stimulated glucose uptake significantly above that seen in the serum obtained from a normal subject. The stimulating activity of the serum completely disappeared following removal of the tumor, since the glucose uptakes of the hemidiaphragms in the patient's postoperative serum were indistinguishable from those seen in the control serum. The glucose uptakes in the preoperative sample were significantly higher than in the postoperative serum.

In the last assay epididymal fat pads were used. The same sample of control serum and the same samples from the patient obtained on June 9 and June 18, used in the second hemidiaphragm experiment, were used again in the fat pad assay. In addition, a sample obtained four months following the operation was assayed. It may be seen that the glucose uptakes of the fat pads were significantly higher in the presence of the preoperative sample than in either the control or in the four month postoperative sample. In this experiment, in contrast to the results obtained with these serums using the hemidiaphragm technic, there were statistically no significant differences between the glucose uptake in the serums obtained just before the operation (June 9) and just after the operation (June 18). Unfortunately, the incubation could not be repeated because the supply of the serums was exhausted.

COMMENTS

The data clearly indicate that the serum from this patient with spontaneous hypoglycemia associated with a retroperitoneal fibrosarcoma contained some factor capable of stimulating the glucose uptake of both the isolated hemidiaphragms of the rat and the epididymal fat pad, and that the stimulating factor disappeared following the removal of the tumor. The stimulation of glucose uptake of the hemidiaphragms of the rat or epididymal fat pad by plasma has usually been interpreted as indicating an increased circulating blood insulin level or insulin-like activity [*9–11*] (see Piazza et al. [*8*] for review).

The serum samples obtained from the patient prior to the operation stimulated the glucose uptake of the hemidiaphragms as much as did the addition of insulin at a level of 0.1 unit per ml. to the normal control serum. We hesitate, however, to assign a specific value of insulin activity in terms of units per milliliter because of the disparity in reports of serum insulin activity from one laboratory to another [*8*].

The nature of the active material in the serum of this patient is of considerable interest. There would appear to be several possibilities. The active substance could be a hitherto unidentified hypoglycemic agent, or even insulin itself, produced by the tumor and released to the systemic circulation. Another possibility is that the tumor in some way stimulated the release of insulin from the pancreas. There was no histologic evidence of increased islet cell activity during a time when the patient was experiencing marked hypoglycemic symptoms, and this would suggest that the pancreas was not the source of the hypoglycemic activity of the serum. It seems likely, therefore, that the tumor produced an as yet unidentified material responsible for the hypoglycemia *in vivo* and the stimulation of glucose uptake *in vitro*.

Studies currently in progress demonstrate that it is possible to extract hypoglycemic material from this tumor. The tumor extract is capable of stimulating the glucose uptake of epididymal fat pads of the rat *in vitro*. This finding lends additional support to the concept that the tumor itself is the source of the insulin-like activity found in the peripheral blood.

SUMMARY

Serum insulin-like activity was estimated by use of the stimulation of glucose uptake of either the hemidiaphragm or epididymal fat pad of the rat as a criterion of increased insulin-like activity. During the time a patient with a large retroperitoneal fibrosarcoma was experiencing severe hypoglycemic episodes her serum insulin-like activity was found by this method of assay to be markedly elevated. The serum insulin-like activity returned to normal levels following surgical removal of the tumor. It is suggested that the tumor was the source of the insulin-like material responsible for the spontaneous hypoglycemia.

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Observations on a Patient with Gaucher's Disease*

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Gaucher's disease is a rare familial disorder characterised by abnormal storage of kerasin in cells of the reticuloendothelial system. Since the first description in 1882 [*1*], about 280 cases were reported up to 1955 [*2*], and many more have been added since. It is not our purpose to review the extensive literature dealing with the clinical [*3–5*], metabolic [*6–8*] and hereditary [*9–11*] features of the disease but to report some observations on a patient who manifested a late leukoerythroblastic reaction.

CASE REPORT

B. S., a forty-six year old Jewish "Ashkenazi" married woman, was admitted to the Medical Department A of the Hadassah University Hospital on December 14, 1958 because of increasing dyspnea and pain in the chest. Family history revealed that the mother died at forty-seven years of age from carcinoma of the uterus. The father, healthy, died in a German concentration camp. One brother is alive and healthy. One sister, mentally retarded, also died in a concentration camp.

The patient was born in Germany. As a child she was small and frail. In 1929, at the age of seventeen, she started to suffer from increasing pain in the left hip joint, thought to be of rheumatic origin; a few months later she could not move the hip. A roentgenogram taken at that time reportedly revealed a deformation of the head of the femur, and a diagnosis of Perthes' disease was made. Six years later pain appeared in the right hip joint, also in the knees, ankles and spine. In 1930 she noticed a swelling in the left upper part of the abdomen which was diagnosed as an enlarged spleen. The spleen continued to increase in size, giving a sense of pressure, heaviness and some pain. In 1935 tonsillectomy, because of recurrent throat infections, was followed by unusually severe bleeding. Because of this and the large spleen, bone marrow aspiration was performed and the diagnosis of Gaucher's disease was established. Photomicrographs of the bone narrow and roentgenograms of the bones were published by Zanardi et al. [*21*]. In 1945 the spleen became so large that it caused serious mechanical difficulties and the patient underwent splenectomy. The spleen weighed 5 kg.; the pathologic examination confirmed the diagnosis of Gaucher's disease. After the operation the patient felt fairly well and was able to lead a moderately active life, although rarely free of pain in her bones and joints. In 1950, when on a visit to Holland, she consulted one of us (J. J. G.) for the first time. The next year she had several infractions of ribs after insignificant trauma. In 1954 and again in 1956 she had a spontaneous fracture of the right humerus, which healed well. Gradually, however, she became more and more incapacitated. She began to lose her teeth and to suffer from frequent epistaxis and ecchymoses. In the last years she tired easily and lost progressively more weight; her legs and arms became very thin but her abdomen increased in size. Treatment during these years was only symptomatic. Because of osteoporosis she was given vitamin D, but without apparent results. A course of testosterone (injected) seemed to relieve her pain but she refused to continue when some hirsutism appeared.

The present illness started on December 12, 1958, with a sore throat, temperature up to 38.2°c. and a severe chill. She complained of pain in her neck and chest and felt as if the chest was compressed by a steel belt, so she could not breathe.

Physical examination revealed a frail woman, looking very ill, in a poor nutritional state. The skin had a diffuse brownish tinge, with flushes on both cheeks. Both conjunctivas showed pingueculae and anemia. The pulse was small, regular, 120 per minute, the jugular veins were congested. The area of cardiac dullness was increased, mainly to the left. On auscultation an accentuation of the second pulmonic sound was found. The blood pressure was 105/60 mm Hg. The diaphragm was pushed upwards, the borders of the lower part of the lung were found in the fourth interspace. The lungs were clear to percussion but on auscultation numerous fine râles were heard at the base of the right lung. A large surgical scar was present in the left quadrant of the abdomen. The liver was very large, extending to the iliac bone on the right, two fingers below the umbilicus in the center, and

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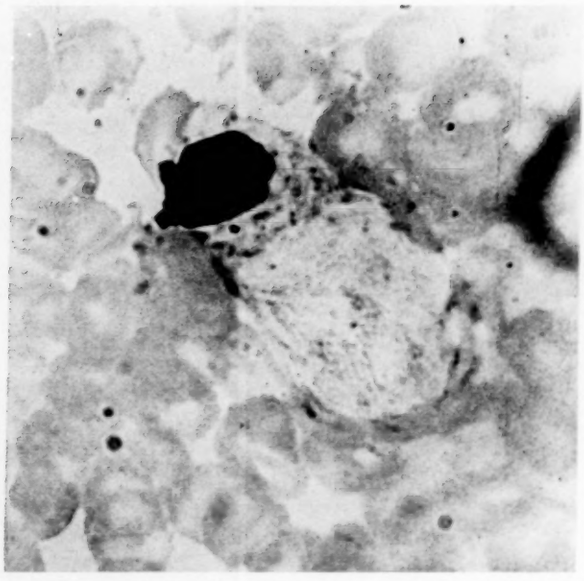

FIG. 1. Typical Gaucher cell in peripheral blood. Original magnification × 1000.

FIG. 2. **Left lateral roentgenogram of the chest** showing massive calcification in the anterior and posterior border of the heart shadow.

crossed the left costal margin in the axillary line; it was very firm in consistency. Movement of both lower extremities, especially rotation and adduction, was limited at the hip joint. Movements of the knees and ankles were normal. Some pitting edema was present around the ankles. The abdominal reflexes were normal. The patellar and ankle reflexes were diminished. No pathologic reflexes were found.

The urine contained 0.2 per cent of protein, a few erythrocytes and leukocytes. The hemoglobin was 12.7 gm. per cent, red cells 4,300,000 per cu. mm., white blood cells 17,800 per cu. mm. with a differential count of 70 per cent neutrophils, 7 per cent band forms, 22 per cent lymphocytes and 1 per cent monocytes. For every hundred white blood cells forty-two normoblasts were counted. Subsequently the number of white blood cells increased to 52,000 per cu. mm. with a ratio of 250 nucleated red cells for every 100 white blood cells. The differential count showed many myelocytes and band forms, and an occasional promyelocyte. Alkaline phosphatase stains of smears of the peripheral blood were strongly positive. On two occasions three typical Gaucher cells were found in the smears of the peripheral blood. (Fig. 1.) In smears from the buffy coat there were many promyelocytes and myelocytes and some cells which were recognized as small Gaucher cells. The thrombocyte count was 136,000 per cu. mm.

The blood urea was 69 mg. per cent, the fasting blood sugar 123 mg. per cent and the serum cholesterol 126 mg. per cent. Results of the cephalin-cholesterol flocculation test were negative. The serum total protein content was 6.1 gm. per cent; a paper electrophoresis analysis gave the following percentual distributions: albumin 23.6, $alpha_1$ globulin 13.2, $alpha_2$ globulin 17.9, beta globulin 18.9 and gamma globulin 26.4 per cent. The serum bilirubin level was 2 mg. per cent; alkaline phosphatase 18.7 Bodansky units; phosphorus 4.5 mg. per cent, calcium 11.3 mg. per cent, uric acid 8.2 mg. per cent. Roentgenographic studies (Dr. M. Frenkel) of the chest revealed an enlarged heart with massive calcification of the pericardium and patchy shadows at the base of the right lung. (Fig. 2.) Roentgenographic studies of the bone disclosed severe deformation of the heads of both femora (Fig. 3) with "Erlenmeyer flask" deformity at the distal ends (Fig. 4), wide areas of decalcification in both iliac bones and in the bones of both lower extremities, with especially severe deformation of the proximal end of the left tibia. Foci of calcification were seen in the distal and proximal ends of both femora and tibias. (Figs. 3 and 4.) A spontaneous fracture with callus formation of the right humerus was also found. Electrocardiograms showed low voltage of the QRS complex and a flattening or inversion of the T waves in the standard leads. In the precordial leads the voltage was normal but the T waves were inverted in all leads.

Pneumonia was suspected and the patient was given Achromycin.® The fever subsided but she continued to complain of dyspnea and pain on movement of the legs. An attempt to influence the course of the disease by the administration of Meticorten® was unsuccessful. The urea increased to 233 mg. per cent, a friction rub appeared over the precordium, and the pulse rate increased to 110. The patient became comatose and died on January 1, 1959.

At autopsy (E. Moran) characteristic changes of Gaucher's disease were found in the liver, lymph nodes, lungs, adrenal cortex and vertebrae, femur, sternum and clavicles. With regard to the erythroblastic reaction observed in the peripheral blood, sections through the diaphysis of the right femur at three different levels revealed almost complete re-

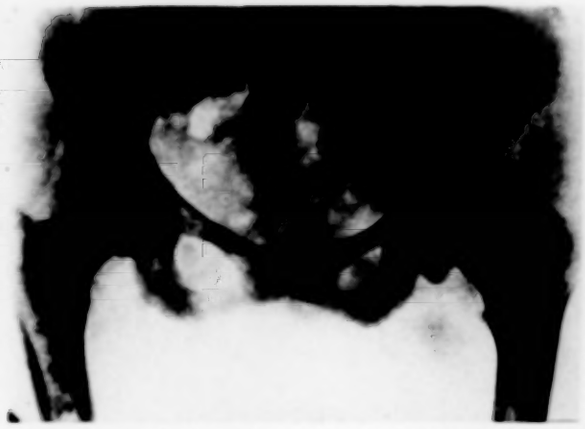

FIG. 3. Severe deformation of the head of both femora, with narrowing of the interarticular space, and irregular shape of the tuberculae in the femoral heads and areas of increased calcification in femoral shafts.

FIG. 4. Erlenmeyer flask deformity of both femora, with deformation of the articular surfaces of both knees and areas of increased calcifications in proximal ends of both tibias.

placement of hematopoietic marrow by fibrous tissue, together with extensive areas of Gaucher cells. In certain areas these cells penetrated the entire thickness of the cortical bone, which appeared atrophic. Here and there small foci of scant hematopoiesis were still preserved and they were found also in some of the Haversian canals. The bone trabeculae in the medulla were atrophic and in many areas focal necrosis was seen. In the vertebrae the findings were very similar. There was marked cortical atrophy, and in the spongiosa extensive fibrous changes were found. Gaucher cells appeared in large groups, with marked atrophy and focal necrosis of the trabeculae. Bone marrow was recognizable only in a few small areas, mixed with fat in varying degree. Similar changes were found in the ribs.

The liver was enlarged (weight 4,860 gm.) and on cut surface exhibited multiple fairly circumscribed nodules of grey greenish soft tissue. In the remaining parenchyma, there was a large coarse network of pale tissue, with disappearance of the lobular structure of the liver. Microscopic examination revealed a nodular parenchyma, with irregular lobular pattern and areas of regeneration. There were many Gaucher cells in the sinusoids and focal fibrosis was present in varying degree. The most striking feature in these areas were multiple foci of hematopoiesis in many sinusoids. (Fig. 5.) Outside the nodules, the liver parenchyma was largely replaced by fibrosis and large clumps of Gaucher cells. No foci of hematopoiesis were seen.

COMMENTS

Gaucher's disease exhibits protean features and great variability in course and severity. The symptoms and signs may start in infancy or childhood and progress rapidly, or they may begin in adolescence, adult, or even late life and progress slowly, with periods of subjective remission and apparent good health [*11*]. The most common localization of the typical Gaucher cells is in the spleen, liver and bone marrow. Less often the lymph nodes [*12*], the kidneys [*13*], the lungs [*14*] and the brain [*15*] are affected.

The variation in the clinical picture is determined by the extent to which each organ is infiltrated by Gaucher cells. The usual clinical picture is that of hepatosplenomegaly, often accompanied by a hemorrhagic diathesis, which is manifested by epistaxis, petechiae and ecchymoses due to thrombocytopenia. When

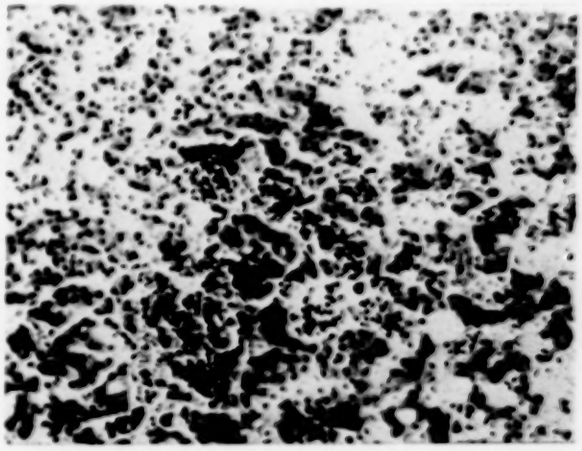

FIG. 5. Extramedullary hematopoiesis in liver, with infiltration of Gaucher cells, hematoxylin and eosin.

the bones are massively infiltrated with Gaucher cells there is a generalized and/or patchy osteoporosis which sometimes leads to spontaneous fractures. Patients may suffer from pain in both bones and joints due to destruction of the articulation. This is sometimes described as the osseous form of the disease. It was subjectively the dominant aspect in our patient. Infiltration of the lungs with Gaucher cells is rare; it may simulate bronchopneumonia clinically and roentgenologically [*14*], as in our patient.

In the present case Gaucher cells were found on two different occasions in smears of the peripheral blood [*15*] and on one occasion in a smear of the buffy coat. These cells were found only at the margin of the smears; this is in accordance with the observation by Groen and Garrer [*4*] that Gaucher cells are found at the periphery of bone marrow smears. In the buffy coat the cells (unlike the "typical" Gaucher cell) were small, their nucleus was in the center and the cytoplasm was not abundant. They could have been confused with reticulum cells but the characteristic folds in the cytoplasm enabled us to identify them as Gaucher cells. Similar cells were seen by Groen in the bone marrow of "carriers" of the disease and described as atypical Gaucher cells. He considered them "probably reticulum cells that have taken up less kerasin and therefore have not changed in type as completely as the typical Gaucher cell" [*4*].

Another unusual feature in this case was the occurrence of a leukoerythroblastic reaction. A small number of normoblasts had been noted in the peripheral blood as early as 1950 but only during the last period of the patient's illness did the number of normoblasts increase markedly. A direct count of the normoblasts performed three days before death showed 29,000 per cu. mm. The number of granulocytes was also increased and among them were myelocytes and promyelocytes. The occurrence of a leukoerythroblastic reaction in Gaucher's disease has been reported only once in the literature [*16*]. In that case, too, it concerned a predominantly osseous type of the disease in a patient with extensive involvement of the liver who had undergone splenectomy. An increase in the number of leukocytes after splenectomy is a well known phenomenon [*17*] in conditions other than Gaucher's disease. We assumed that the leukoerythroblastic reaction in our case was due not only to the absence of the spleen but also to replacement of the bone marrow by Gaucher cells and the occurrence of foci of extramedullary hematopoiesis. The positive alkaline phosphatase staining supported this assumption, and the autopsy proved it by demonstrating extensive destruction of the bone marrow and replacement by Gaucher cells and fibrotic tissue. There were numerous foci of ectopic hematopoiesis in the liver.

Most authors agree that Gaucher's disease is due to a metabolic disturbance, namely, the production of a glucosidocerebroside instead of the usual kerasin, which is a galactosidocerebroside [*8*]. According to one hypothesis the body, unable to excrete or degrade the abnormal analogue, has to store it in the reticuloendothelial cells. Consequently, when the spleen is removed, as in our case, the total production of the glucosidocerebroside has to be stored in the remaining parts of the reticuloendothelial system, that is, in the liver and bone marrow.

Liver function in Gaucher's disease usually remains adequate in spite of extensive infiltration by Gaucher cells [*18*]. In our case there was some hepatic dysfunction which manifested itself in an increased serum bilirubin and a disturbed electrophoretic pattern of the serum proteins. Evidence of hepatic dysfunction was also found in the patient reported on by Melamed and Chester, in whom a leukoerythroblastic reaction also showed [*16*]. The high serum alkaline phosphatase in our patient was present as early as 1950; it was probably due in part to increased activity of the osteoblasts trying to repair the damage to the bone, as also manifested by the presence of areas of sclerosis in the shafts of the lower extremities. The low value of blood cholesterol is a conspicuous feature in Gaucher's disease and is as yet unexplained. Diabetes has been described in some cases of Gaucher's disease [*19*]; in our case the diabetes was rather mild. The connection between the two conditions is not clear.

The origin of the extensive calcification of the pericardium is not clear. Histologic examination did not reveal a definite cause. A culture obtained after death revealed Diplococcus pneumoniae in the pericardial fluid. The patient had received large quantities of vitamin D in the past in an attempt to improve her osteoporosis and this might have contributed to the calcification. It is also possible that as a result of her hemorrhagic diathesis the patient had had an

unrecognized hemorrhage into the pericardial cavity, with organization and deposition of calcium.

The patient, although married for more than twenty years, had no children. We would like to use this opportunity to add a few remarks on the aspects of heredity in Gaucher's disease. Many of the patients previously described by one of the present authors (J. J. G.) [*4*] were killed in the gas chambers of the Auschwitz concentration camp, so that only a small number could be followed up. But the experience with these few survivors and with some new patients supports the hypothesis that the disease starts as a mutation which is inherited as a single dominant characteristic, which means that in large enough families about half the sibs were found to be affected. No evidence of any sex-linked inheritance has come to light so far. Furthermore, not a single instance has been observed in which a healthy member of a family in which Gaucher's disease occurred, transferred it to his offspring.

In an earlier paper [*9*] the hypothesis was formulated that the so-called "horizontal spread" of the disease is due to the fact that the first mutation disturbs the cerebroside metabolism so slightly that the affected persons do not show symptoms and signs until late in life, and then in a mild degree only. However, it seems that the disease tends to become more severe in the successive generation. Whereas carriers detected only by a biopsy specimen obtained from the sternum were found to transfer the disease in marked degree to part of their offspring, all the severely ill patients have either produced healthy children or no children at all. Not a single patient with Gaucher's disease was born of a father or mother with manifest disease. This supports the suggestion that 50 per cent of the offspring of a patient with severe disease inherit the mutation, but in them the metabolic disturbance is so severe as to be incompatible with even embryonic life. From this it follows that patients with manifest Gaucher's disease can at least be freed from worry about their offspring. They can be told with reasonable assurance that they need not fear that their children will have their illness; they can expect either healthy children or none at all. Therefore, the question whether such a patient should marry or not need not be decided on the basis of the possible danger for the offspring.

Finally, we wish to point out that this patient was an "Ashkenazi" Jewess. This means that she belonged to those groups of Jews who, as far as can be historically ascertained, lived in Western, Central and Eastern Europe during the centuries of their exile. This is in contrast to the so-called Sephardic Jews who lived in exile mainly in Southern Europe, North Africa and the Middle East. (Groups of both communities have moved since to other parts of the world.) It is becoming increasingly evident that Gaucher's disease is not only many times more frequent among Jews than among other ethnic groups, but that this predilection is restricted almost entirely to the Ashkenazi Jews, so that among Sephardic Jews it is almost as rare as among non-Jews [*20*]. This interesting fact indicates that the Jews are racially not so homogenous as is commonly supposed, and not all the differences among them can be explained by intermixing with other ethnic groups among whom they lived. If this were so, Gaucher's disease would be expected to be frequent also among non-Jews in Western, Central or Eastern Europe, which is not the case. Could it be that the specific inheritance of a tendency to develop the "Gaucher mutation" was a characteristic of one of the tribes who formed the Jewish people in biblical times, and that this tribe emigrated more or less as a whole to Europe when conditions in their own country became unbearable?

SUMMARY

A patient with Gaucher's disease is described in whom Gaucher cells were found in the peripheral blood and who manifested a leukoerythroblastic reaction many years after splenectomy. The mode of inheritance of Gaucher's disease is discussed.

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Pituitary Apoplexy*

Report of Two Cases, with Pathological Verification

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IN 1950 Brougham, Heusner and Adams [*1*] collected from the literature five cases of pituitary apoplexy and added five cases of their own. Headaches, ophthalmoplegia, amblyopia, stupor and coma of sudden onset in a patient with signs or history of a pituitary adenoma are the presenting symptoms. Often the distinction from infarction of the mesencephalon may be difficult but correct diagnosis is of paramount importance because of the dramatic response to endocrine replacement therapy and surgical intervention for relief of compressive symptoms possible in some cases. Two new cases, with pathological verification, are reported here and the pertinent literature is briefly reviewed.

CASE 1. A sixty-two year old white widowed housewife (M. I. R., P.B.B.H. 9K792) was admitted to the Peter Bent Brigham Hospital in May 1957. Ten years previously she had been told that she had "gland trouble." Her family had noted that her nose had become enlarged and that her glove size had changed from 5½ to 7 at about age eighteen; no other changes were noted in subsequent years. Menopause occurred at age forty-eight. There was no complaint of headache, visual disturbance or deepening of the voice. Her daughter stated that the patient's memory and mental acuity had steadily decreased in the preceding several years.

Physical examination revealed normal vital signs and a blood pressure of 210/120 mm. Hg. The patient obviously had acromegaly (Fig. 1) with a large nose, a "lantern jaw" and spade hands. The skin was normal. Bilateral, non-tender depressions were present in the parietal bones. The tongue was large. The heart was enlarged, with a grade 1 parasternal systolic murmur. The tip of the spleen could be felt 2 cm. below the left costal margin. The liver was palpable 4 fingerbreadths below the right costal margin and both kidneys were palpable. Cranial nerves were intact, except for slight flattening of the left nasolabial fold without true weakness. No field defect could be plotted on confrontation or by perimetry. No motor weakness was noted although many muscles were small. There was no median nerve weakness. Reflexes were all present and hypoactive, with the exception of the ankle jerks which were absent, and the plantar responses were bilaterally flexor. There was slight loss to vibration sense distally in the legs.

Results of the blood Hinton test were negative. The urine was within normal limits. The hematocrit was 36 per cent. The total eosinophil count was 147 per cu. mm. and the white blood count was normal. The serum iron was 48 μg. per cent. The blood urea nitrogen was 8 mg. per cent, total protein 6.1 gm. per cent with 3.9 gm. of albumin, the fasting blood sugar was 78 mg. per cent with a two-hour postprandial sugar of 151 mg. per cent, the serum cholesterol was 175 mg. per cent, sodium 144 mEq. per L., potassium 4.3 mEq. per L., CO_2 31 mEq. per L., chloride 113 mEq. per L., calcium 5.2 mEq. per L., phosphorus 1.5

FIG. 1. Case 1. Facial appearance at age sixty-three.

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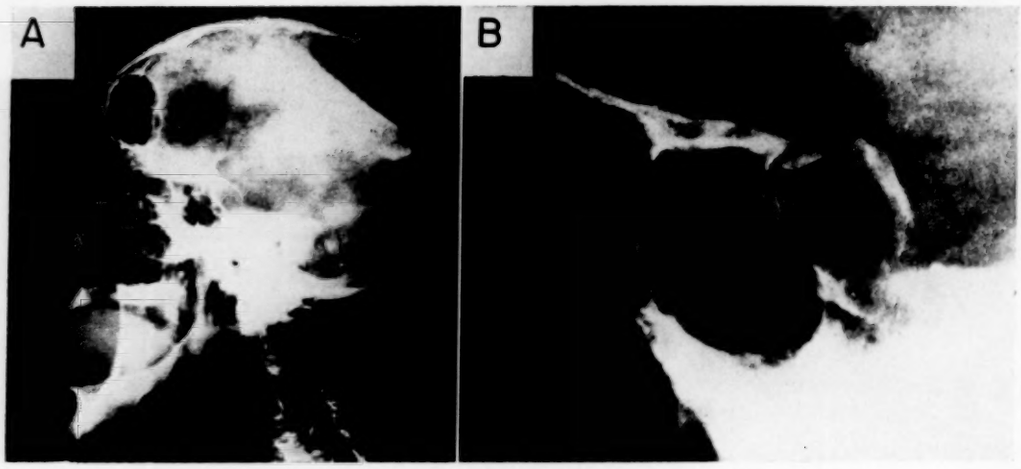

FIG. 2. Case 1. A, lateral roentgenogram of skull. B, enlarged view of sella turcica.

mEq. per L., alkaline phosphatase 3.4 Bodansky units, creatinine 0.8 mg. per cent. Results of an intravenous glucose tolerance test were within normal limits. A urinary phosphorus clearance measurement revealed normal reabsorption of phosphate in the tubules. Protein-bound iodine was 10 and later 6.8 μg. per cent, and radioactive iodine uptake was 44 and 38 per cent. Red blood cell radioactive iodine was normal. FSH was positive at 5 mouse units and 100 mouse units, and negative at 200 mouse units. The electrocardiogram showed left ventricular hypertrophy with frequent premature ventricular beats. Chest roentgenograms revealed pulmonary emphysema and questionable pulmonary hypertension. Roentgenograms of the hands disclosed a marked increase in calcium content and tufting of terminal phalanges. The skull films showed an abnormal sella turcica with undercutting of the anterior clinoids and some erosion of the dorsum sella with preservation of the posterior clinoids. There were large frontal sinuses, a prominent mandible and biparietal depressions. (Fig. 2.)

In view of the borderline increase of thyroid function and increase of serum phosphorus the question of tumor activity was raised. It was decided to treat the patient with radiation. She received an estimated depth dose to the pituitary of 1,930 r.

Fourteen months later the patient returned for gallbladder surgery. Since radiation to her pituitary there had been no increase in the size of her nose, hands, feet or jaw. There was no change in vision. There had been some deterioration of mental status and she could not remember the date or the day of the week. She could name presidents to Hoover, and was oriented to place and person. The remainder of the neurologic examination was as previously. Perimetric examination showed no change in visual fields.

The blood urea nitrogen was 17 mg. per cent, sugar 76 mg. per cent, sodium 140 mEq. per L., potassium 4.2 mEq. per L., CO_2 28.6 mEq. per L., chloride 96 mEq. per L., calcium 5.2 mEq. per L., phosphorus 1.4 mM. per L. and alkaline phosphatase 4.5 Bodansky units. Roentgenograms of the skull were unchanged.

The patient underwent a cholecystectomy and common duct exploration. Acute and chronic cholecystitis with cholelithiasis and dilation of the cystic duct were found.

Ten days following discharge from the hospital the patient returned with a complaint of recurrent "nervousness." She had had a retro-orbital headache, more marked on the right side, for one week. On examination she was in mild congestive heart failure. The neurological status was unchanged. On the fourth hospital day she experienced several episodes of hemoptysis, and became slightly confused. She received 25 units of ACTH for the next two days. Two days later hemorrhage recurred, the patient became lethargic and somnolent, then shock developed. One hundred fifty cubic centimeters of clotted blood was aspirated from the pharynx. She was treated for shock but remained arreflexic and flaccid throughout. The pupils were miotic, equal and totally unresponsive to light. There was no change in the electrocardiograms. The hematocrit was 38 per cent, the blood sugar was 258 mg. per cent, blood electrolytes were normal. During the next several hours bilateral extensor plantar responses developed. The following morning hydrocortisone, 100 mg., was added to the intravenous fluids, and 5 per cent carbon dioxide and 95 per cent oxygen mixture was started. At this point the patient awoke and began to respond to verbal command. Lumbar puncture revealed an opening pressure of 95, and yielded xanthochromic fluid with 52 red blood cells in the first tube, 40 red blood cells in the third tube; no crenated cells were present, no white cells, total protein 22 mg. per cent, reaction to the Pandy test was negative.

Later that day the patient was lethargic but responsive. She was dysarthric and there were pooled

secretions in the nasopharynx. The neck was supple, the carotids pulsated bilaterally. The eyelids were puffy, the visual fields were grossly full, the discs were flat but the veins in the right fundus were full. The eyes moved in all directions but neither abducting eye reached the outer canthus. There was a 15 degree divergent squint at rest. The pupil on the right was 3 mm., that on the left 2 mm., and both reacted to light directly and consensually. Slight ptosis was present on the left and there was weakness of eye opening bilaterally. The corneal reflex was decreased on the right and there was decreased response to pin prick in the first division of the trigeminal nerve. The remainder of the cranial nerves were intact. There was a moderately severe quadriparesis. All limbs were flaccid, the left side was affected more than the right. Tendon reflexes were absent throughout. There were bilateral extensor plantar responses, the right more markedly so than the left. Sensation was grossly intact. Acute hemorrhagic necrosis of a pituitary adenoma was considered to be the most likely possibility. The patient was maintained on supportive therapy but died one week after admission to the hospital.

Autopsy was performed seventeen hours after death. The body measured 162 cm. and weighed 50 kg. The cranial bone depressions measured 8 by 5 by 1.5 cm. on the left, 6 by 4.5 by 1.5 cm. on the right. The thickness of the cranial bones at the depressions was 0.2 cm. The lungs were heavier than normal and congested. The heart weighed 600 gm., the liver 2,000 gm., the pancreas 160 gm. The kidneys were normal except for congenital lobulation. The spleen weighed 400 gm. It had normal trabeculations without prominence of lymphoid follicles. The right adrenal weighed 14 gm. and the left 13 gm. The cortices measured 1 mm. bilaterally. The thyroid weighed 92 gm.; the left lobe was markedly enlarged (65 gm.) and presented a nodular surface with numerous small cysts, the right lobe weighed 27 gm. and revealed small nodulation of the surface. The parathyroids appeared normal.

The pituitary was an ovoid dark red-gray mass weighing 2 gm. On sections the gland presented a hemorrhagic surface, more extensively on the right side. The cut surface was semitranslucent and brown, with multiple cyst formation, and was traversed by fibrous tissue. The sella turcica measured 2 cm. in width, 1.7 cm. in depth and 1.3 cm. in the anteroposterior diameter. The right side of the sella turcica was wider than the left. The spheroid sinus was covered by blood and mucus and a small erosion in the posterior wall of the left sphenoid sinus communicated directly with the sella turcica. The brain weighed 1,300 gm. and presented no abnormality in gross configuration. The meninges were normal. There was no abnormality of the basal vessels.

On microscopic examination the adrenal cortex was slightly increased in thickness and there was focal lymphocytic infiltration in the medulla. The thyroid follicles were lined by flattened or cuboidal epithelium and contained colloid, with some increase of interstitial fibrous bands. The parathyroid consisted of clear cells and a few eosinophilic cells. The pituitary gland contained eosinophilic cells surrounded by thin fibrous bands. Basophilic cells were seen. The acidophilic tumor showed areas of ischemic and hemorrhagic infarction. In some areas cellular response was minimal but elsewhere lymphocytic and polymorphonuclear cells were prominent, especially along the edge of areas of necrosis and hemorrhage. Amorphous eosinophilic material and red blood cells infiltrated parts of the tumor. The changes were more marked in the right lobe. In one section a thrombus was present in a small vein. Those areas of the capsule that were visualized were normal. The point of extracapsular extension of hemorrhage was not identified. Red blood cells infiltrated the meninges. Representative sections of the brain were within normal limits.

Summary: A sixty-two year old woman with a ten year history of acromegaly and a three year history of mental deterioration received x-ray therapy to the pituitary one year before death. Two weeks prior to death headaches abruptly developed; the patient had episodes of hemoptysis and became confused, unresponsive and quadriparetic. Pupils were unequal; there was a bilateral sixth nerve paralysis, a left third nerve palsy and involvement of the first division of the fifth nerve on the right. A presumptive diagnosis of hemorrhagic necrosis of the pituitary was made. Postmortem examination revealed a hemorrhagic eosinophilic pituitary tumor, which had eroded the posterior wall of the sphenoid sinus. There was no compression of intracranial structures. Thrombosis of a small vein was noted in relation to the infarcted tumor. (Retrospectively, the hemopytsis was probably secondary to bleeding from the tumor into the sphenoid sinus and nasopharynx.)

CASE II. A fifty-seven year old married Negro man (B. C. H.,* 1587355) came to the hospital because of sudden loss of vision in both eyes on the day before. He had noticed decreased libido for four years, with loss of axillary, facial and genital hair and the development of gynecomastia. Three weeks before admission he had intermittent headaches, which became very severe two days prior to admission and were unrelieved by medication. The day prior to admission his right eye was noted to be closed and the headache had decreased in intensity. Examination on the accident

* This patient was seen by one of us (S. L.) during work in the Neuropathology Laboratory of the Mallory Institute of Pathology. We are grateful to Dr. Joseph M. Foley for permission to report this case.

floor revealed a blood pressure of 180/70 mm. Hg, pulse of 104, respirations of 40 and temperature of 106.4°F. The patient was obese, with fine skin, and looked much younger than his stated age. He was semistuporous, breathing rapidly, and had a hot dry body but cold arms, legs, hands and feet. Body and facial hair was sparse, the breasts were slightly enlarged bilaterally. There was no apparent vision in either eye. The right pupil was 2 mm. larger than the left and did not respond to light. The left pupil responded to light directly and consensually. There was ptosis and a fixed dilated pupil on the right and a suggestion of atrophy of the optic disc. The left eye roved, the pupil was reactive. The neck was stiff to forward flexion. Corneal reflex on the right was decreased. There was no apparent motor weakness or prominent sensory loss. Bilateral grasping and sucking were present. The patient was disoriented to time and place; his speech was slow, slurred and difficult to understand. He had difficulty concentrating on questions but obeyed simple commands. The chest was clear. The heart was within normal limits. The liver was palpable 1 fingerbreadth below the right costal margin. The testes were atrophic and the penis small.

Laboratory studies revealed a hematocrit of 60 per cent, a white blood count of 13,050 per cu. mm. with a normal differential. The reaction to a serologic test for syphilis was positive, the blood non-protein nitrogen was 28 mg. per cent, CO_2 was 18.9 mEq. per L., chloride 92 mEq. per L., sodium 130 mEq. per L., potassium 4.3 mEq. per L. Roentgenograms of the skull revealed marked enlargement of the sella turcica which was depressed so that it completely occupied the sphenoid sinus. Shortly after admission both discs were noted to be hyperemic with a small hemorrhage on the right optic nerve head. The right eye was fixed in the mid-line with jelly-like movements in response to rapid head turning. There was slight spasticity in the left arm and in both legs. Knee and ankle jerks were absent and the plantar reflex was bilaterally unresponsive. Lumbar puncture was not performed. The patient was treated symptomatically with alcohol sponges and refrigeration blanket, and was given chlorpromazine and 50 units of ACTH. The temperature rose to 107°F. two hours after the patient was placed in the refrigeration blanket. Immediate neurosurgical intervention was planned but before transfer could be arranged, the patient died.

At autopsy the body was that of a well developed, well nourished Negro man; it weighed 240 pounds and measured 180 cm. in length. Body hair was sparse, and there was no gynecomastia. The lungs appeared normal. The spleen weighed 350 gm. The gastrointestinal tract was within normal limits. The pancreas weighed 145 gm., the liver was pale, firm and weighed 2,140 gm., the right kidney weighed 170 gm., the left 185 gm. The thyroid weighed 18 gm. Two parathyroids were found, measuring 0.9 by 0.3 by 0.4 cm. The right adrenal weighed 3.5 gm., the left adrenal 4 gm., and the cortices of both were thinner than normal. The testes weighed 4 gm. each and the parenchyma could not be stretched more than 1 cm. The prostate and external genitals were conspicuously small.

In the sella turcica there was a walnut-sized tumor which measured 4.5 by 7.5 by 7 cm. It extended quite far anteriorly but the bony walls of the sella turcica were intact. A thin dural partition covered the bulging tumor and was apparently the remnant of the diaphragma sella.

On section the tumor showed necrosis and hemorrhage. Grossly there was no evident normal pituitary tissue. The fresh weight of the brain was 1,400 gm. and it was symmetrically swollen. No local areas of hemorrhage, softening or depression were noted. A fibrous opacity was present in the leptomeninges at the base and extended beneath the brain stem. The optic chiasm bulged upward and was broader anteroposteriorly than usual. The leptomeninges on the superior and inferior surface of the chiasm were fibrotic. The right anterior cerebral artery had been displaced upward and somewhat to the right. There had been some upward and lateral displacement of the posterior portion of the left gyrus rectus and there was grooving of the superior surface of the left optic nerve which could have been produced by the anterior cerebral artery. The mamillary bodies were not compressed and the third nerves had been displaced laterally against uncal herniations. There was no posterior grooving of the medial surface of the temporal lobes. The cerebrum was sectioned in the horizontal plane. The third ventricle was distended to three or four times the normal size. There had been no perforation of the floor, although the tuberal region had been displaced upward when viewed from the basal surface. There were transventricular adhesions of both anterior horns in their lowermost portions. The lateral ventricles were slightly distended, with no displacement. There was no invasion of the brain by tumor. The brain stem and cerebellum appeared normal on section. The posterior portion of the left gyrus rectus was compressed upward and possibly infarcted. The optic chiasm showed a zone of grayish softening centrally which extended more to the left side and involved the left optic tract behind the chiasm.

On microscopic examination, the testicular tissue was characterized by marked loss of seminiferous tubules, with decreased cellularity and very few active cells of the spermatogenic series. Few Leydig cells were seen. The adrenals showed a moderate general decrease of vacuolization. There was a marked amount of fat separating the tissue of the parathyroids, but the cells appeared normal. The thyroid epithelium was low and there was a large amount of colloid in the acini.

The pituitary tumor was almost completely

destroyed by necrosis and hemorrhages. There were large numbers of polymorphonuclear leukocytes within the tumor mass and in the adjacent leptomeninges of the chiasmal region; there were some polymorphonuclear leukocytes in the ependyma of the third ventricle. Some normal pituitary tissue was attached to part of the tumor. The optic nerves showed some loss of fibers in their central portic ns. There was fiber loss and gliosis within the chiasm to which the necrotic tumor was attached.

Summary: A fifty-seven year old Negro man entered the hospital because of sudden bilateral blindness following severe headache. Upper cranial nerve signs developed and the patient rapidly became comatose and died. There was a previous history suggesting hypopituitarism and roentgenograms revealed an enlarged sella turcica. Autopsy revealed a chromophobe adenoma that was necrotic and hemorrhagic. There was evidence of compression of adjacent basal structures.

The presenting complaint of sudden blindness is attributed by some to intracapsular confinement of the hemorrhage, and can be alleviated on occasion by rapid neurosurgical decompression of the bulging tumor capsule.

COMMENTS

It has been suggested that vascular lesions in pituitary adenomas result from the tumor outgrowing its blood supply [*2,3*] or are "due to thrombosis or perhaps compression of veins" [*4*].

The vascular supply of the pituitary is derived from the internal carotid artery by way of the superior and inferior hypophysial arteries, the superior arising extracavernously, the inferior within the cavernous sinus [*5*]. Anastomoses from these vessels form a ring supplying the neural lobe and infundibular stem, but no arterial branches from either division supply the pars distalis [*5*], which receives its entire blood supply by the long portal vessels from the neural hypophyseal stalk, and the short portal vessels from the lower infundibular stem [*6,7*]. Most of the afferent blood supply to the anterior lobe is derived from the long portal vessels [*8*] and experimental infarction of the anterior pituitary has been produced in the rat by cauterization of the portal vessels [*9*]. In Case 1 a single thrombosed vein was seen, suggesting that venous thrombosis may have been of importance.

Trauma has been suggested as one factor productive of hemorrhage in the pituitary, with [*10*] or without [*11*] an associated tumor, although no postmortem verification was available in the former case. Intense estrogen therapy has been held responsible for pituitary apoplexy [*12*]. Radiation has been suggested as etiologically productive of bleeding within the tumor mass [*2–16*]. Case reports are available of bleeding into a pituitary tumor during the course of radiation in pathologically proved [*17–20*] and clinical [*21,22*] cases.

The sudden appearance of extraocular muscle palsy with the onset of hemorrhage has been commented on frequently [*2,3,23,24*] and early surgery has been advocated for preservation of vision [*16,19,20,25,26*]. Blindness may be a striking part of the clinical picture [*2,3*]; it has been suggested that loss of vision results from intracapsular rather than extracapsular hemorrhage [*19*].

Spinal fluid findings have varied from heavily blood stained [*27*], in a case which was not pathologically proved, to "blood tinged fluid under pressure" [*28*]. Spinal fluid pressure may be elevated [*29*], protein may be increased [*1,3*], sugar may be decreased [*3*], and there may be pleocytosis and xanthochromia [*1,2,3,30*]. A normal cerebrospinal fluid, however, does not preclude the diagnosis. The spinal fluid formula may be compatible with spontaneous subarachnoid hemorrhage, and on occasion the clinical picture may suggest ruptured aneurysm [*31*] or other vascular syndromes [*32*]. The occurrence of pupillary abnormalities, vomiting, drowsiness, coma. Cheyne-Stokes respirations and rising temperature [*33*] may be suggestive of basilar infarction, an alternative that could not be excluded with certainty on a clinical basis in Case 1. Sudden death may occur without evident bleeding [*34–36*], or survival following presumed hemorrhage may be of long duration [*37*]. Indeed, it has been suggested that intrasellar simple cysts may represent puerperal necrosis in an adenoma [*38*].

General supportive measures and aggressive endocrine replacement therapy are indicated during the acute stages of pituitary apoplexy. In some instances active neurosurgical intervention to remove acutely swollen tumor tissue and blood clot may be life-saving [*39*].

SUMMARY

Two cases of pituitary apoplexy, with pathological verification, are presented and the literature is briefly reviewed.

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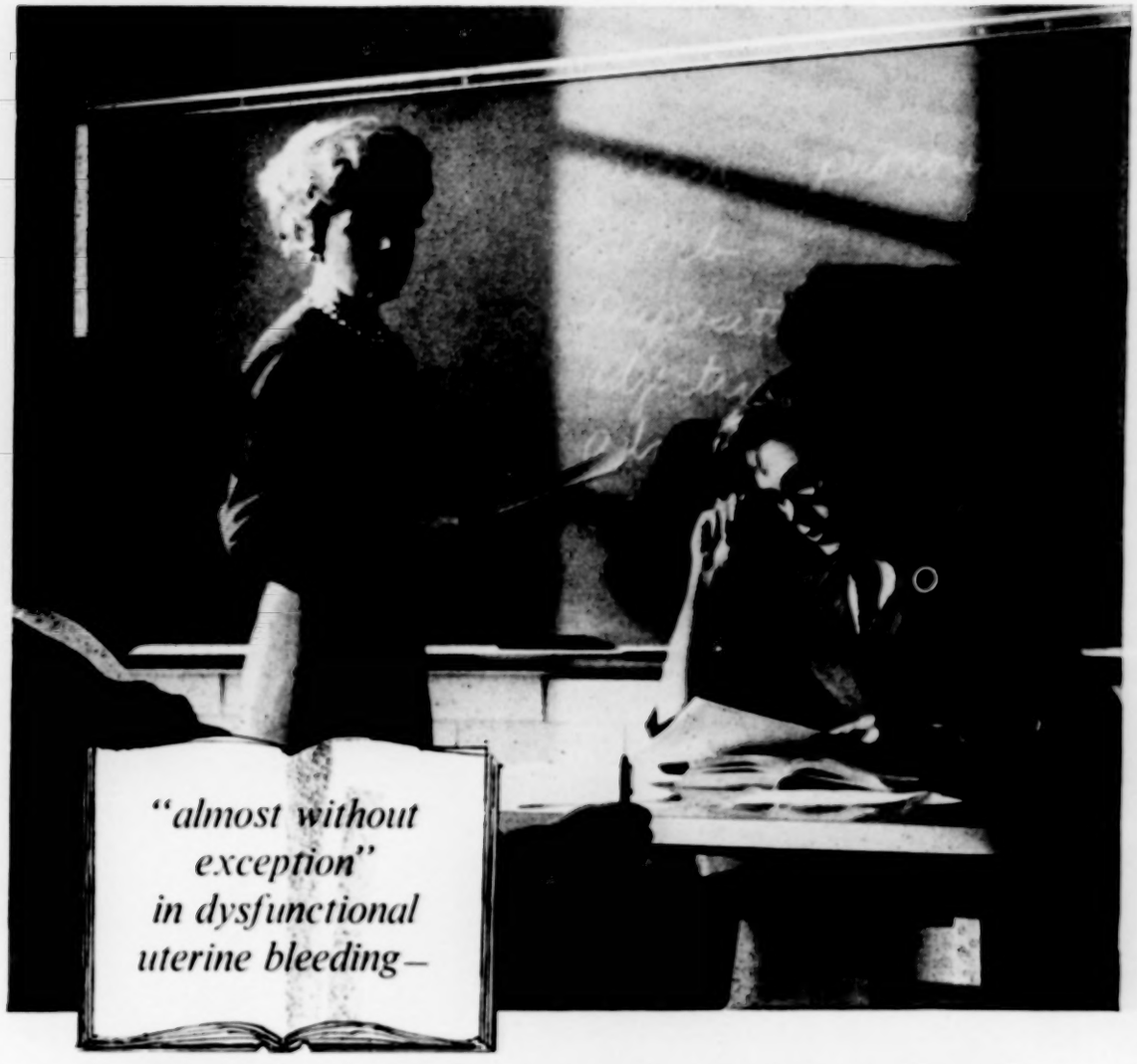

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During adolescence, the menopause or whenever deficient or irregular elaboration of progesterone leads to menorrhagia or metrorrhagia the potent progestational activity of Enovid may be relied on to exert prompt and definite hemostatic action. Moreover, Enovid may be prescribed without the risk of inducing hirsutism or other virilizing effects.

"Dysfunctional bleeding can, almost without exception, be controlled with hormonal therapy," Southam[1] asserts and continues, "norethynodrel (Enovid) . . . will produce hemostasis within 24 hours. . . ."

Dosage and Supply: *In menorrhagia*, 20 mg. daily for four or five days, reduced to 10 mg. through day 25. If the period is still menorrhagic, the same dosage schedule should be repeated; if normal, 10 mg. daily should be given from day 5 to day 25 through two or three succeeding cycles. *In metrorrhagia*, 10 or 20 mg. of Enovid daily until day 25 to control bleeding. The determined dosage should be continued daily from day 5 to day 25 for two or three consecutive cycles and then withdrawn to determine whether the menstrual cycle has returned to normal. Enovid (brand of norethynodrel with ethynylestradiol 3-methyl ether) is supplied in uncoated, scored, coral-colored tablets of 10 mg. each.

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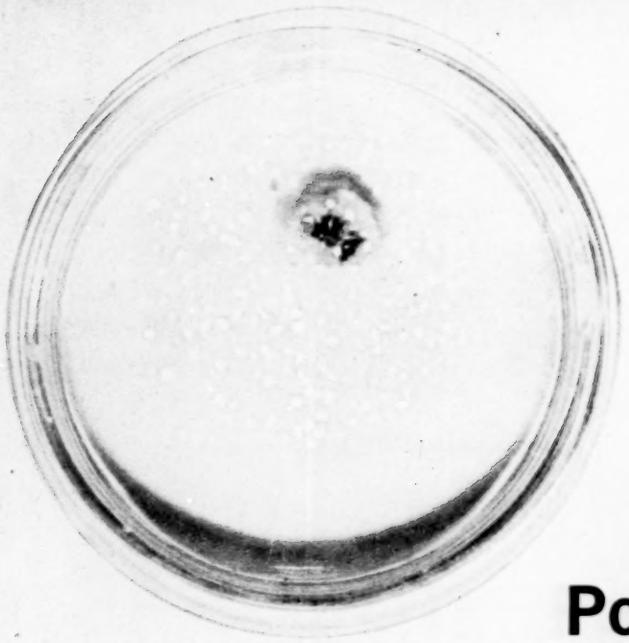

Potassium Penicillin V versus semi-synthetic penicillin

Recent clinical evidence sheds new light on some important questions...

Q. Which of the two oral penicillins provides greater antibacterial activity?
In a follow-up study[1] of oral penicillins, McCarthy and Finland compared the antibacterial activity of potassium penicillin V and semi-synthetic penicillin. They said: "Penicillin V provided greater activity than phenethicillin [semi-synthetic penicillin] against the streptococcus and pneumococcus, at least equivalent activity against the staphylococcus and sarcina in the serum and the same or greater activity in the urine . . ."

In another study[2], Griffith found that penicillin V not only produced peak levels of serum antibacterial activity faster, but produced values almost half again as high as those obtained with semi-synthetic penicillin.

A direct laboratory comparison[3] by Abbott scientists revealed a measurable difference in activity, milligram for milligram, between the two penicillins *in vitro*. Against four pathogenic strains (staphylococcus, streptococcus, pneumococcus, and corynebacterium species), potassium penicillin V exhibited from two to eight times the antibacterial activity of semi-synthetic penicillin.

Q. How valid are blood levels as a basis for comparison?
In comment on the two penicillins, McCarthy and Finland state[1]: "Thus, although the claim of better absorption and excretion and higher serum level of phenethicillin may be partly correct, strictly speaking, this is true in a very restricted sense and is therapeutically meaningless. Indeed the claim is misleading since it clearly implies greater antibacterial and presumably curative activity, which, in fact, the drug does not possess . . . "

Q. Are there useful differences in resistance to penicillinase?
In another recent report[4], Geronimus commented: "Very large concentrations [of semi-synthetic penicillin] . . . were required to inhibit even so-called

moderately penicillin-resistant staphylococci when populations were employed that approached those found *in vivo*. Inferences regarding the possible effectiveness of phenethicillin in infections by penicillinase-producing staphylococci drawn by others from experiments with relatively minute inocula were found to be unwarranted."

McCarthy et al.[5] reached a similar conclusion: "Both of these penicillins [potassium penicillin V and phenethicillin] are qualitatively similar to penicillin G in their susceptibility to penicillinase produced by *Staphylococcus aureus*."

At Abbott, investigators studying the same subject[3] found that the rate of destruction of all three penicillins was so great that any differences were of no therapeutic significance.

Q. How does the safety of oral penicillins compare?

While surveys[6] have established that oral penicillin produces fewer and less severe reactions than does injectable penicillin, to date no clinical studies have produced any evidence that one oral form is less allergenic than another.

Q. What about recent editorials on oral penicillin?

Recently, New England Journal of Medicine editorialized[7]: "It thus appears that the major claims of phenethicillin over penicillin V are not well founded. More data are needed to permit a complete comparison of these and other penicillins, particularly in their effects on infections caused by penicillinase-producing staphylococci, but it is fair to say that the new, so-called synthetic penicillin possesses no demonstrated virtue of importance that should impel one to choose over other available forms."

And in England, where semi-synthetic penicillin was first discovered and marketed, *British Medical Journal* editorialized[8]: "There is no evidence of any activity superior to that of other penicillins against Gram-negative species, and what differences there are against sensitive species are in favour of penicillin G or V or both; this applies to all varieties of streptococci tested."

Q. What are the benefits of Compocillin-VK?

Compocillin-VK is Abbott's potassium penicillin V. It offers early, high concentrations of serum antibacterial activity against penicillin-sensitive organisms. Following appropriate doses, initial activity levels are higher than those obtained with intramuscular penicillin G. Available in easy-to-take forms for any age: tiny Filmtab® tablets, 125 mg.; and 250 mg.; or as granules for tasty cherry-flavored Oral Solution.

COMPOCILLIN®-VK

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(POTASSIUM PENICILLIN V)

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Inflammatory reaction following stress!

In inflammation, either localized or generalized in nature, capillary damage – increased permeability, resulting in seepage of blood constituents into the tissues – is a uniform basic reaction resulting from injury or stressors of various types:

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DISEASE STATES: Viral, bacterial, malignancies, endocrine

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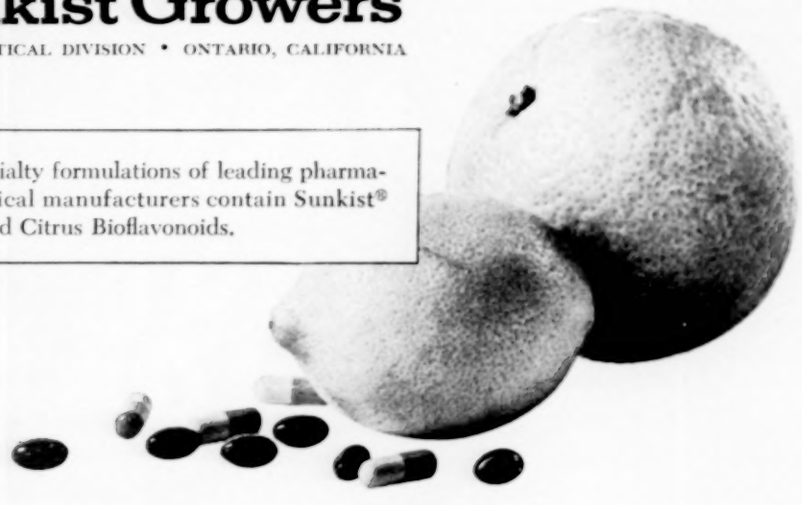

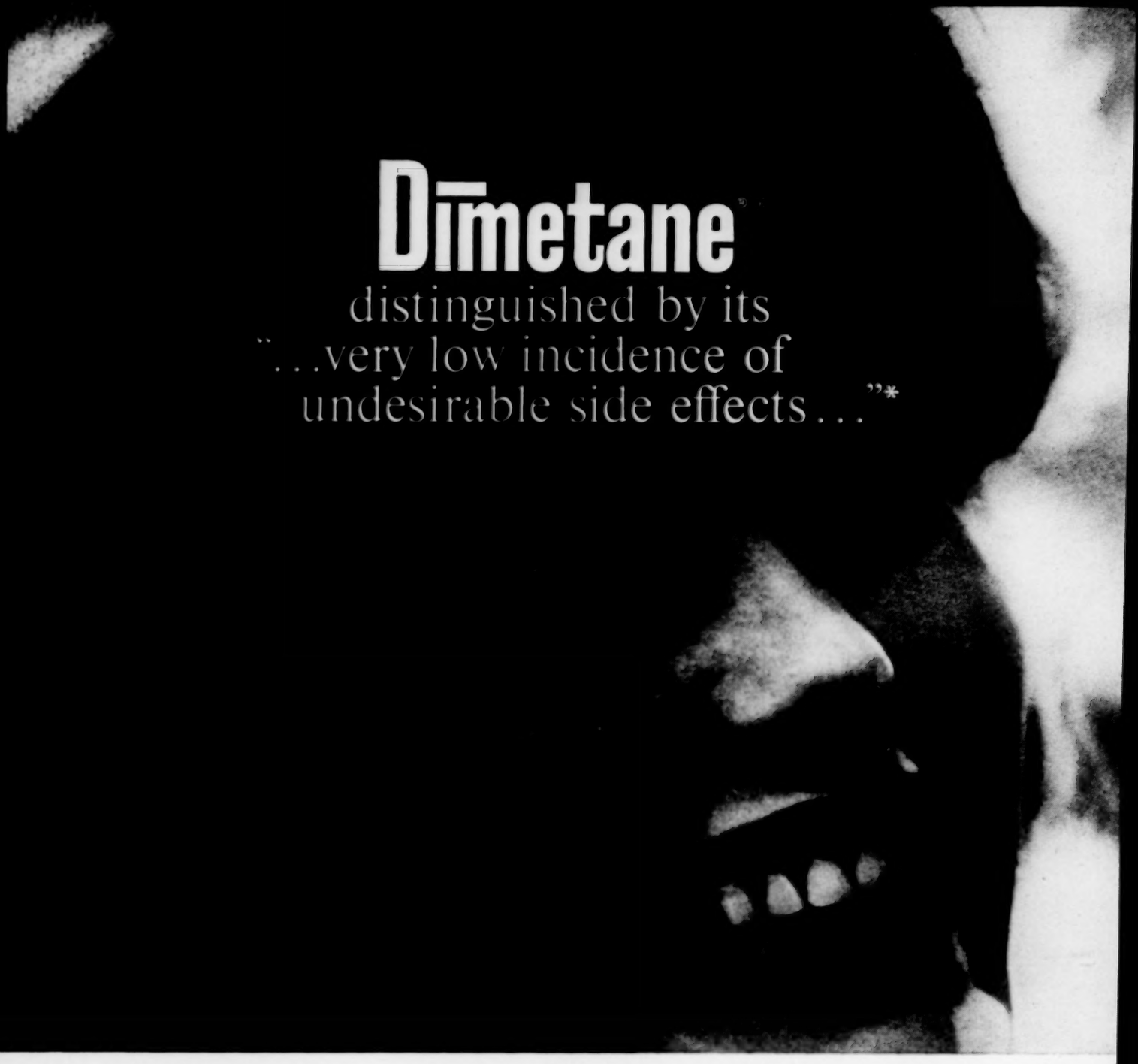

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distinguished by its
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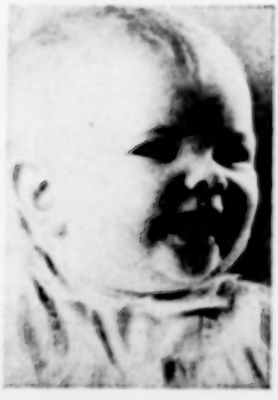
even in allergic infants



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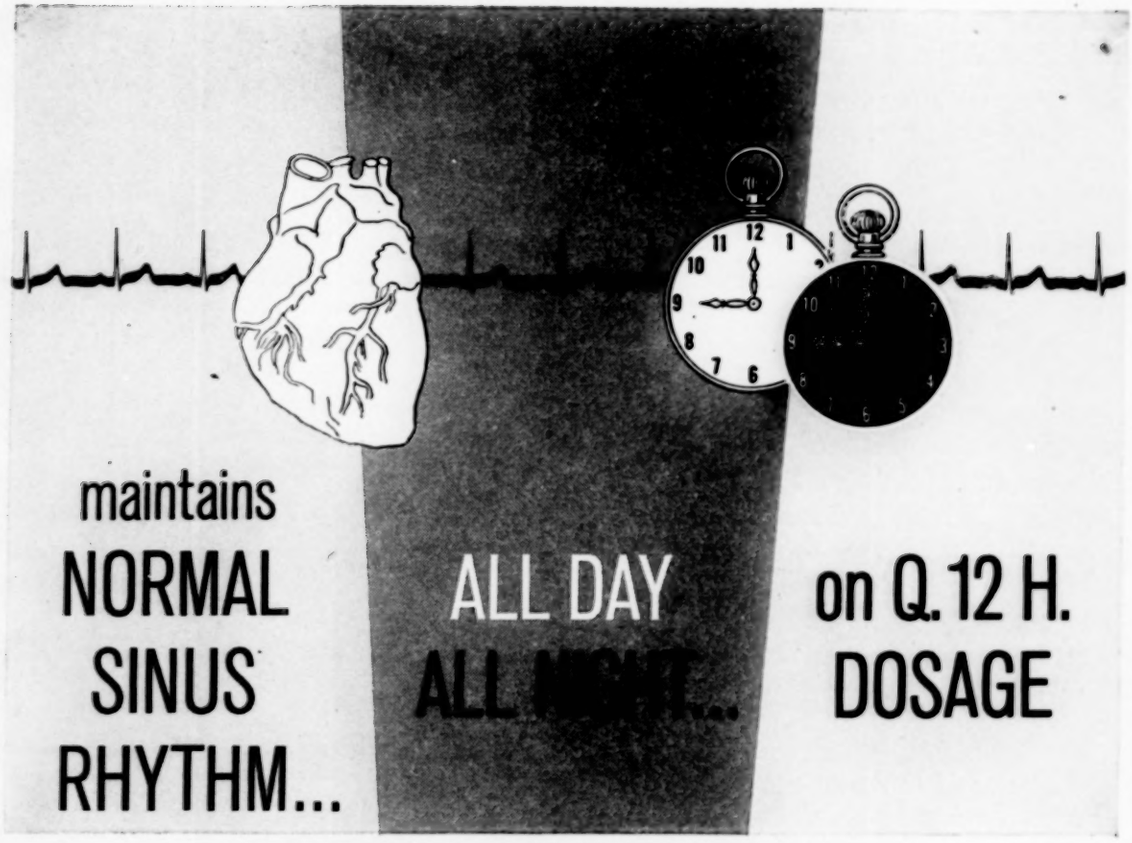

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For SAMPLES and complete literature[1-10] giving indications, cautions, etc., write

REFER TO PDR Page 821

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This concept is clearly stated in the following quotation from a recent JAMA editorial: "It is accepted generally that specific alteration in the diet will lower the concentration of cholesterol in the blood. The most effective results to date have been achieved by increasing consumption of polyunsaturated fatty acids, particularly linoleic acid." "A particular regimen will be effective only if polyunsaturated fatty acids are responsible for an appreciable percentage of the total fat calories. That is, they must replace rather than supplement some of the saturated fats and oils already in the diet."[1]

In spite of this clear and unbiased statement, the advertising of some margarines seems designed to mislead physicians and their patients by capitalizing on the publicity given to corn oil as the principal source of linoleic acid. The following ambiguous claims are typical:

According to the headline:

The margarine is made of 100% Corn Oil. Buried in the body copy are the words partially hydrogenated.

Misleading because:

The partial hydrogenation has largely converted linoleic acid into saturated fats and into monounsaturated oleic acid, which has been observed to have no effect on serum cholesterol.

According to the headline:

Some claim to have twice the corn oil nutritional benefit of any other leading spread.

Misleading because:

Such a statement obviously implies that this margarine has twice as much linoleic acid, hence greater cholesterol-lowering effect. The truth is that you can buy a margarine with significantly higher linoleic acid content in drugstores.

And so it goes. Literature sent to physicians and journal ads to the profession have been equally misleading. For example, *references being cited refer to clinical studies with a totally different product.* No wonder the author of the editorial cited above felt compelled to warn physicians about "widespread misinformation in this field!"

We don't like such misleading advertising, and we don't use it to promote Emdee Margarine. We're content to deal in facts:

- **Emdee Margarine contains significantly more linoleic acid than other corn oil margarines currently marketed—and contains significantly less of the unnatural trans isomer forms of fatty acids.**
- **Emdee Margarine—and only Emdee Margarine—was used in clinical evaluation studies, even though others now cite the references.**
- **Emdee Margarine—and only Emdee Margarine—has published reports of its value in cholesterol-lowering diets, including articles in JAMA[2], Geriatrics[3], and American Journal of Clinical Nutrition[4].**

Corn oil margarines are *not* alike. They vary greatly in percentage of the active ingredient—linoleic acid. Of them all, Emdee Margarine has far more linoleic acid. It's true that our patented linoleic acid-sparing process makes Emdee Margarine more expensive. But, it's *worth more* when you want your patient's serum cholesterol to go down.

Although the misleading promotion of some margarines may confuse some of your patients, we feel certain that it will not deceive the critical physician—and that you will continue to depend, as you always have, on the facts and on your own clinical evaluation of your patient's needs.

PITMAN-MOORE COMPANY
DIVISION OF ALLIED LABORATORIES, INC., INDIANAPOLIS 6, INDIANA

EMDEE®
margarine

References: 1. Pollack, H.: J.A.M.A. *172*:1165 (Mar. 12) 1960. 2. Boyer, P. A.; Lowe, J. G.; Gardier, R. W., and Ralston, J. D.: J.A.M.A. *170*:257 (May 16) 1959. 3. Terman, L. A.: Geriatrics *14*:111 (Feb.) 1959. 4. Jolliffe, N.; Rinzler, S. H., and Archer, M.: Am. J. Clin. Nutrition *7*:451 (July-Aug.) 1959.

special process protected by
U. S. Patent No. 2,890,959

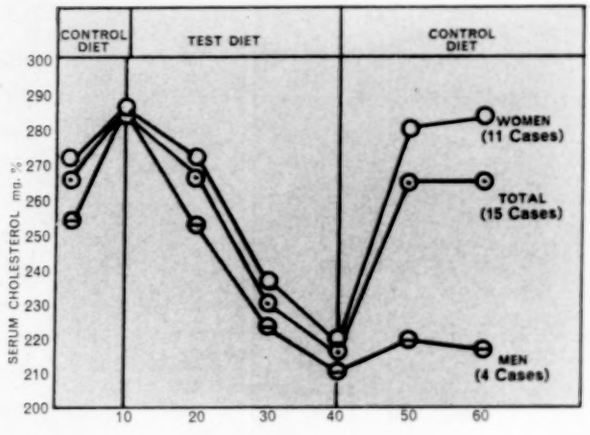
(SEE OTHER SIDE FOR ADDITIONAL INFORMATION ON EMDEE MARGARINE)

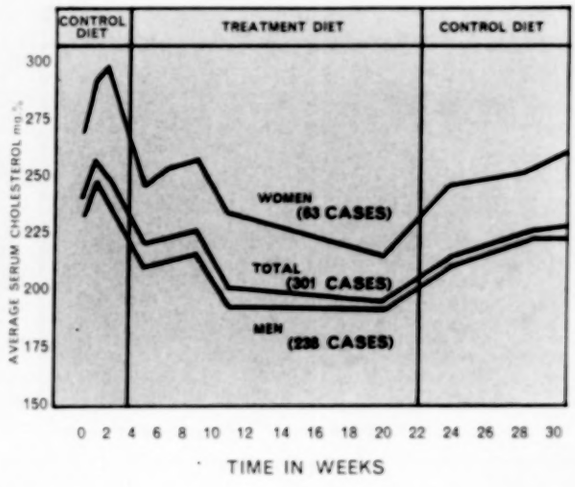
Corn oil margarines are *not* alike in linoleic acid content and, therefore cannot all be of equal value in lowering serum cholesterol. Emdee Margarine contains *significantly more linoleic acid* than any other corn oil margarine currently marketed. Emdee Margarine is the *only* margarine with published scientific reports of its value in reducing serum cholesterol.

Serum cholesterol goes down

when Emdee Margarine is substituted for spreads and shortenings containing more saturated or hydrogenated fatty acids.

Emdee Margarine in place of other spreads and shortenings has been shown to be a practical way to lower serum cholesterol without complicating or creating a weight reduction problem. Emdee provides effective levels of linoleic acid. In clinical studies, patients accepted Emdee Margarine without reservation. Results of these studies indicate Emdee's effectiveness:





"Average serum cholesterol values were noticeably reduced during the test diet, becoming statistically significant at the end of the second ten-day period and showing increasing significance at the end of the third ten-day period."[1]

"In a nine-month study of over 300 inpatients in a state institution, it was found that a regimen employing a nonhydrogenated corn oil margarine (Emdee Margarine) for other solid fats as the principal dietary alteration was effective in achieving and maintaining a reduction in blood cholesterol levels."[2]

References: 1. Terman, L. A.: Geriatrics *14*:111 (Feb.) 1959. 2. Boyer, P. A.; Lowe, J. G.; Gardier, R. W., and Ralston, J. D.: J.A.M.A. *170*:257 (May 16) 1959.

When You Want to Lower Blood Cholesterol

EMDEE® *margarine*

PITMAN-MOORE COMPANY
DIVISION OF ALLIED LABORATORIES, INC., INDIANAPOLIS 6, INDIANA

To protect flavor and texture, Emdee Margarine is packaged in cans and kept under constant refrigeration. The linoleic acid-sparing manufacturing process is covered by U. S. Patent No. 2,890,959.

New, more effective analgesic

Kills pain.....stops tension

For neuralgias, dysmenorrhea, upper respiratory distress, and postsurgical conditions—new compound of Soma, phenacetin and caffeine kills pain, stops tension, reduces fever—gives more complete relief than other analgesics...acts fast, relief lasts four to six hours.

NEW NONNARCOTIC ANALGESIC

soma® Compound

Composition:
Soma (carisoprodol), 200 mg.;
phenacetin, 160 mg.;
caffeine, 32 mg.
Dosage: 1 or 2 tablets q.i.d.
Supplied: Bottles of 50
apricot-colored, scored tablets.

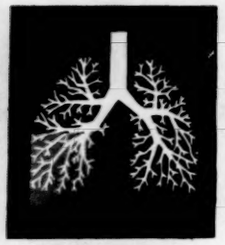
References available on request.

WALLACE LABORATORIES
Cranbury, N. J.

NEW FOR MORE SEVERE PAIN

soma® Compound + codeine

BOOSTS THE EFFECTIVENESS OF CODEINE: Soma Compound boosts the effectiveness of codeine. Therefore, only ¼ grain of codeine phosphate is supplied to relieve the more severe pain that usually requires ½ grain. **Composition:** Same as Soma Compound plus ¼ grain codeine phosphate. **Dosage:** 1 or 2 tablets q.i.d. **Supplied:** Bottles of 50 white, lozenge-shaped tablets; subject to Federal Narcotics Regulations.



when the allergy is more than antihistamines alone can control...and intensive steroid therapy alone is more than the allergy requires...

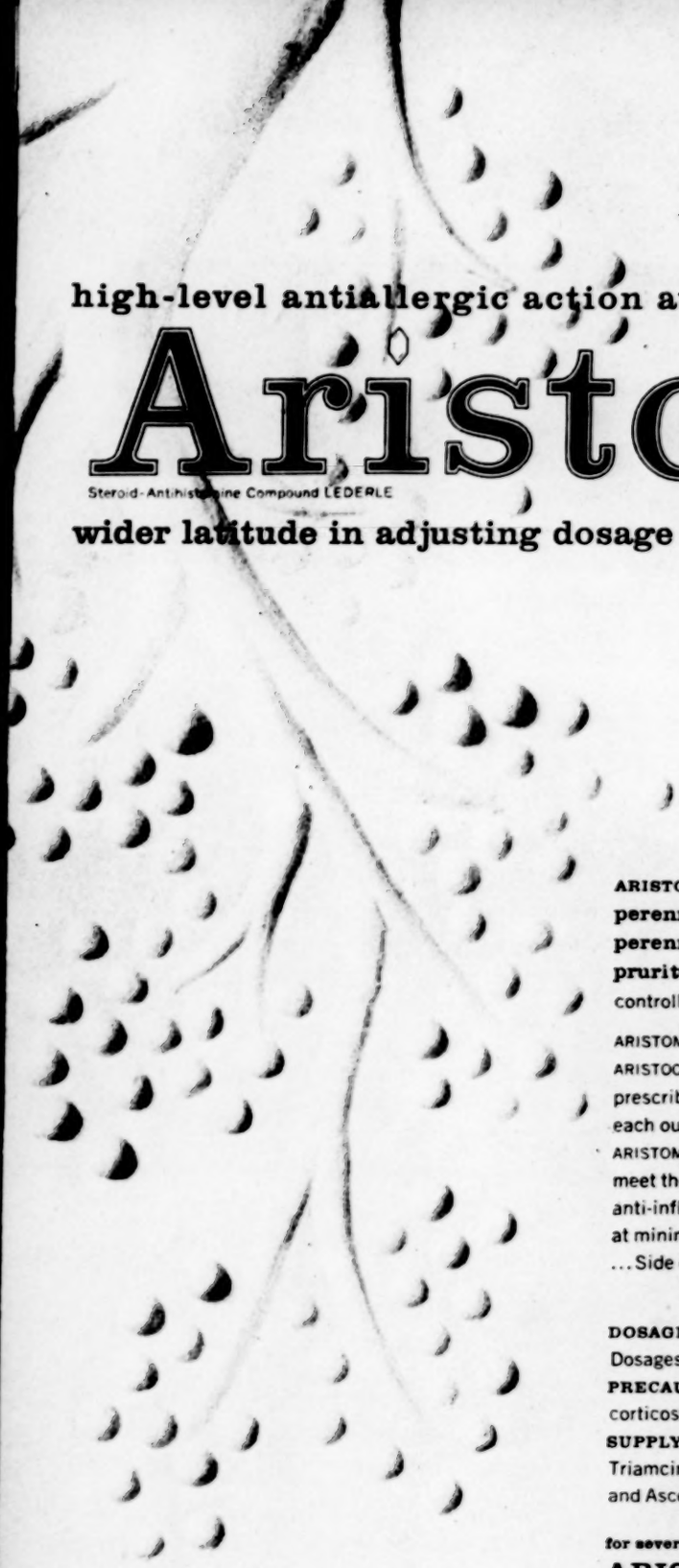
high-level antiallergic action at low-level drug intake...

Aristomin®

Steroid-Antihistamine Compound LEDERLE

CAPSULES

wider latitude in adjusting dosage for better tolerated therapy



ARISTOMIN IS PARTICULARLY ADVANTAGEOUS IN: perennial asthma, allergic, seasonal or perennial rhinitis, drug reactions, allergic pruritus, hay fever, which may be too severe to be controlled by antihistamines alone.

ARISTOMIN combines the corticosteroid efficacy of ARISTOCORT® Triamcinolone with the action of the widely prescribed antihistaminic, chlorpheniramine. Supplying each outstanding component at the lowest effective dosage, ARISTOMIN permits widest latitude in adjusting therapy to meet the individual patient's requirement. Offers combined anti-inflammatory—antiallergic—antihistaminic action at minimal maintenance levels. Well-tolerated. ...Side effects infrequent and minor in nature.

DOSAGE: One to eight capsules a day in divided doses. Dosages should be based on individual therapeutic response.
PRECAUTIONS: All customary precautions pertaining to corticosteroid therapy should be observed.
SUPPLY: Each ARISTOMIN Capsule contains ARISTOCORT Triamcinolone (1 mg.), Chlorpheniramine Maleate (2 mg.), and Ascorbic Acid (75 mg.). Bottles of 30 and 100.

for severe allergies requiring full-scale steroid therapy

ARISTOCORT® Triamcinolone

1 mg. scored tablets (yellow); 2 mg. scored tablets (pink); 4 mg. scored tablets (white); 16 mg. scored tablets (white).

Request complete information on indications, dosage, precautions and contraindications from your Lederle representative or write to Medical Advisory Department.

A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

what TWISTON does for your allergy patient

TWISTON®

rotoxamine

takes him out of this class: zzzzzzzzz zzzzzzzzzzzzzz zzzzzzzzzzzzzz

puts him into this class: !!!!!!!!!!!!!! !!!!!!!!!!!!!!!!!!!!!!!!!!!! !!!!!!!!!!!!!!!!!!!!!!!!!!!!!!

TWISTON is "tailor-made" to keep your allergy patient alert. Twiston is unsurpassed for symptom control. Twiston is effective in *unusually* low dosage: has a prolonged duration of action—drowsiness rarely occurs. No toxicity reactions reported.

TWISTON
. . . anti-allergic
. . . anti-side effects

available as:
Tablets TWISTON, 2mg.
Tablets TWISTON R-A
***(Repeat Action Tablets),* 4mg.**

McNEIL *McNeil Laboratories, Inc., Philadelphia 32, Pa.*

U.S. PATENT PENDING

Put your low-back patient back on the payroll

Soma relieves stiffness –stops pain, too

YOUR CONCERN: Rapid relief from pain for your patient. Get him back to his normal activity, fast!

HOW SOMA HELPS: Soma provides direct pain relief while it relaxes muscle spasm.

YOUR RESULTS: With pain relieved, stiffness gone, your patient is soon restored to full activity—often in days instead of weeks.

> Kestler reports in controlled study: *Average time for restoring patients to full activity: with Soma, 11.5 days; without Soma, 41 days.* (*J.A.M.A. Vol. 172, No. 18, April 30, 1960.*)

Soma is notably safe. Side effects are rare. Drowsiness may occur, but usually only in higher dosages. Soma is available in 350 mg. tablets. **USUAL DOSAGE: 1 TABLET Q.I.D.**

The muscle relaxant with an independent pain-relieving action

SOMA®

(carisoprodol, Wallace)

Wallace Laboratories, Cranbury, New Jersey

Butazolidin

Proved by a decade of experience

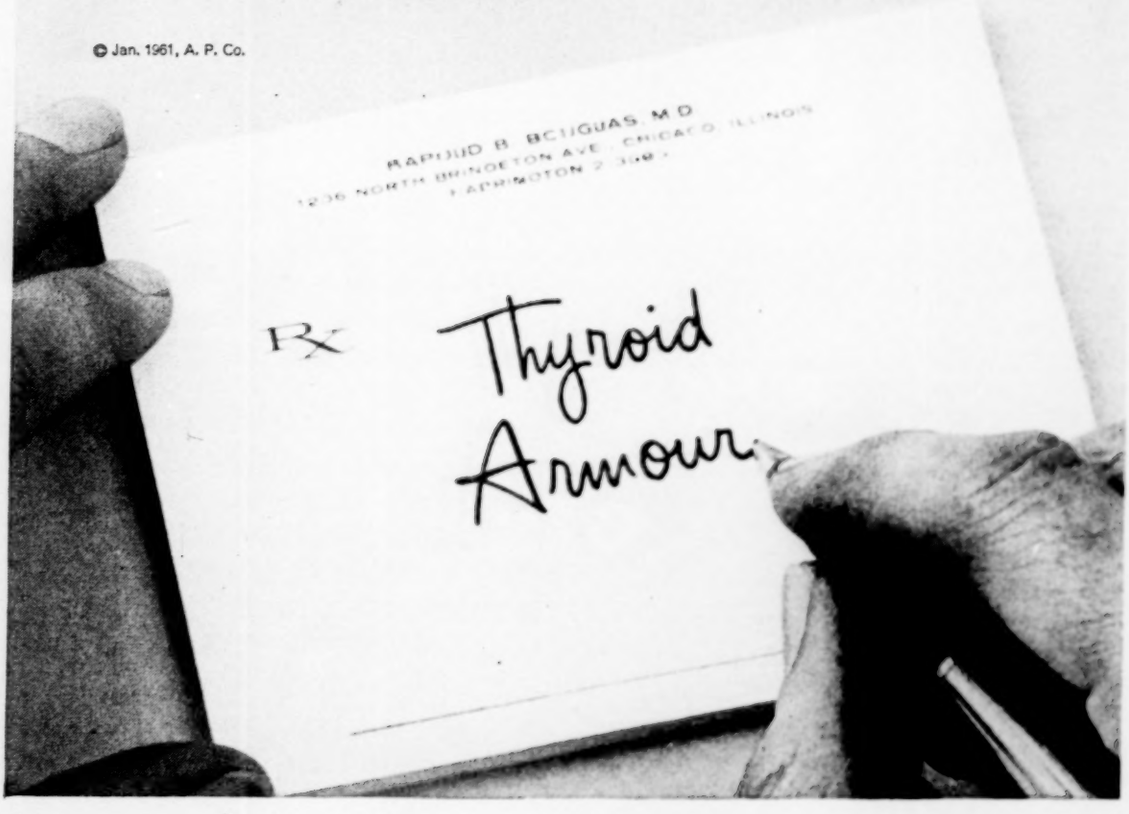
only 2 seconds to specify MAXIMUM QUALITY

It takes only 2 seconds to specify "THYROID ARMOUR" on a prescription blank, yet these words represent the highest grade thyroid available, manufactured with all the control skills learned during three-quarters of a century of experience with endocrine products. THYROID ARMOUR is the original standard of comparison for all thyroid preparations, and is regarded throughout the world as the quality thyroid product.

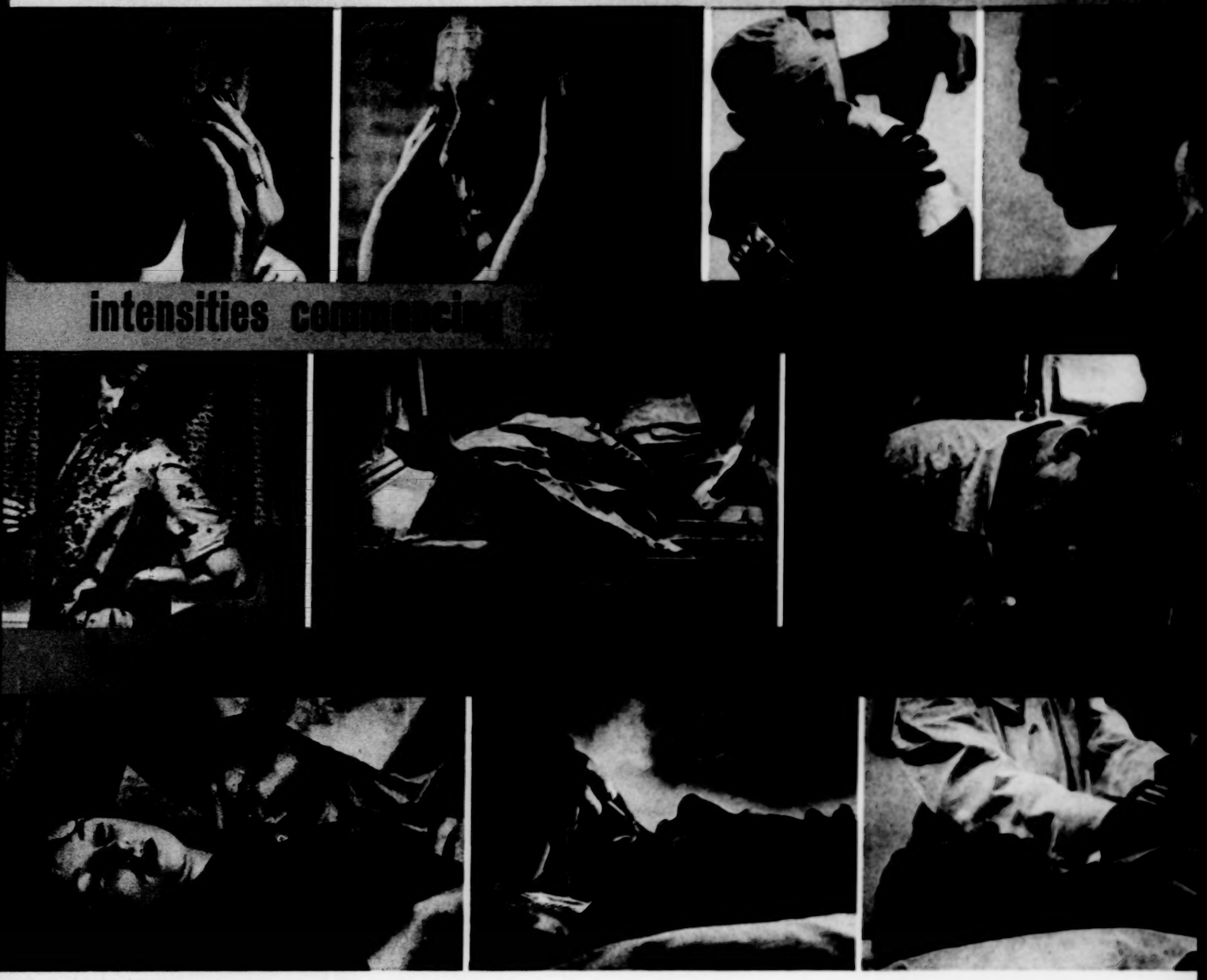
THYROID U.S.P.

Thyroid Tablets (Armour) are prepared from fresh selected glands, desiccated and standardized by official U.S.P. method to contain 0.2 per cent of iodine in thyroid combination. Thyroid Powder U.S.P. (Armour) is standardized and of uniform potency. USES: Thyroid deficiencies, cretinism, myxedema, nodular goiter (non-toxic), non-nodular goiter. A variety of clinical conditions will respond to the use of Thyroid (Armour) when subclinical hypothyroidism is involved, i.e., gynecologic conditions such as functional menstrual disorders, sterility, habitual abortion; recurring conjunctivitis; certain types of anemias and obesity; and certain changes which occur in hair, skin and fingernails. DOSAGE: ¼ to 5 grains daily as required by clinical condition. Therapeutic effect develops slowly and lasts for two months or longer. Thus the daily dose may be given as a single dose (preferably in the morning) rather than several times daily. Patients treated with thyroid should be continuously under the physician's observation. CONTRAINDICATIONS: Heart disease and hypertension, unless the metabolic rate is low. SUPPLIED: Tablets—bottles of 100, 1000 and larger: potencies of ¼, ½, 1, 2 and 5 grains. Powder—1 oz. 4 oz., and 1 lb. bottles.

ARMOUR PHARMACEUTICAL COMPANY
KANKAKEE, ILLINOIS *Armour Means Protection*



Percodan tablets effectively relieve pain through a range of



intensities commencing

Percodan®

(Salts of Dihydrohydroxycodeinone and Homatropine, plus APC)

TABLETS

for pain

prompt **relief**
profound **relief**
prolonged **relief**

ACTS FASTER—usually within 5-15 minutes. **LASTS LONGER**—usually 6 hours or more. **MORE THOROUGH RELIEF**—permits uninterrupted sleep through the night. **RARELY CONSTIPATES**—excellent for chronic or bedridden patients.

AVERAGE ADULT DOSE: 1 tablet every 6 hours. May be habit forming. Federal law permits oral prescription.

Each PERCODAN* Tablet contains 4.50 mg. dihydrohydroxycodeinone hydrochloride, 0.38 mg. dihydrohydroxycodeinone terephthalate, 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. acetophenetidin, and 32 mg. caffeine.

Also available—for greater flexibility in dosage—PERCODAN®-DEMI: The PERCODAN formula with one-half the amount of salts of dihydrohydroxycodeinone and homatropine.

LITERATURE AVAILABLE ON REQUEST

Endo

ENDO LABORATORIES
Richmond Hill 18, New York

*U.S. Patent Nos. 2,628,185 and 2,907,768

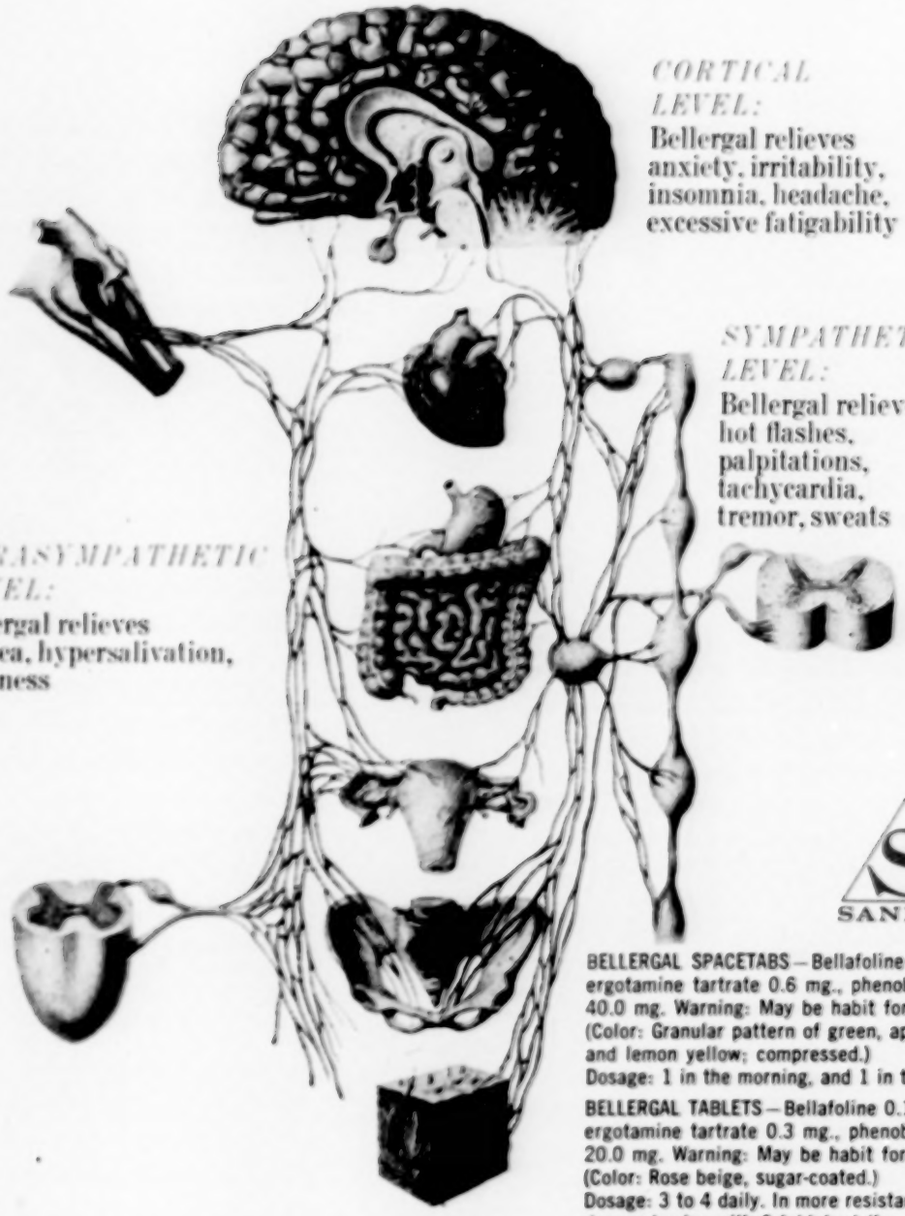
Menopausal distress: a syndrome involving all three levels of the autonomic nervous system

for functional disorders of the menopause Bellergal®

SPACETABS®

stabilizes the entire autonomic nervous system

(without disturbing endocrine balance)



CORTICAL LEVEL:
Bellergal relieves anxiety, irritability, insomnia, headache, excessive fatigability

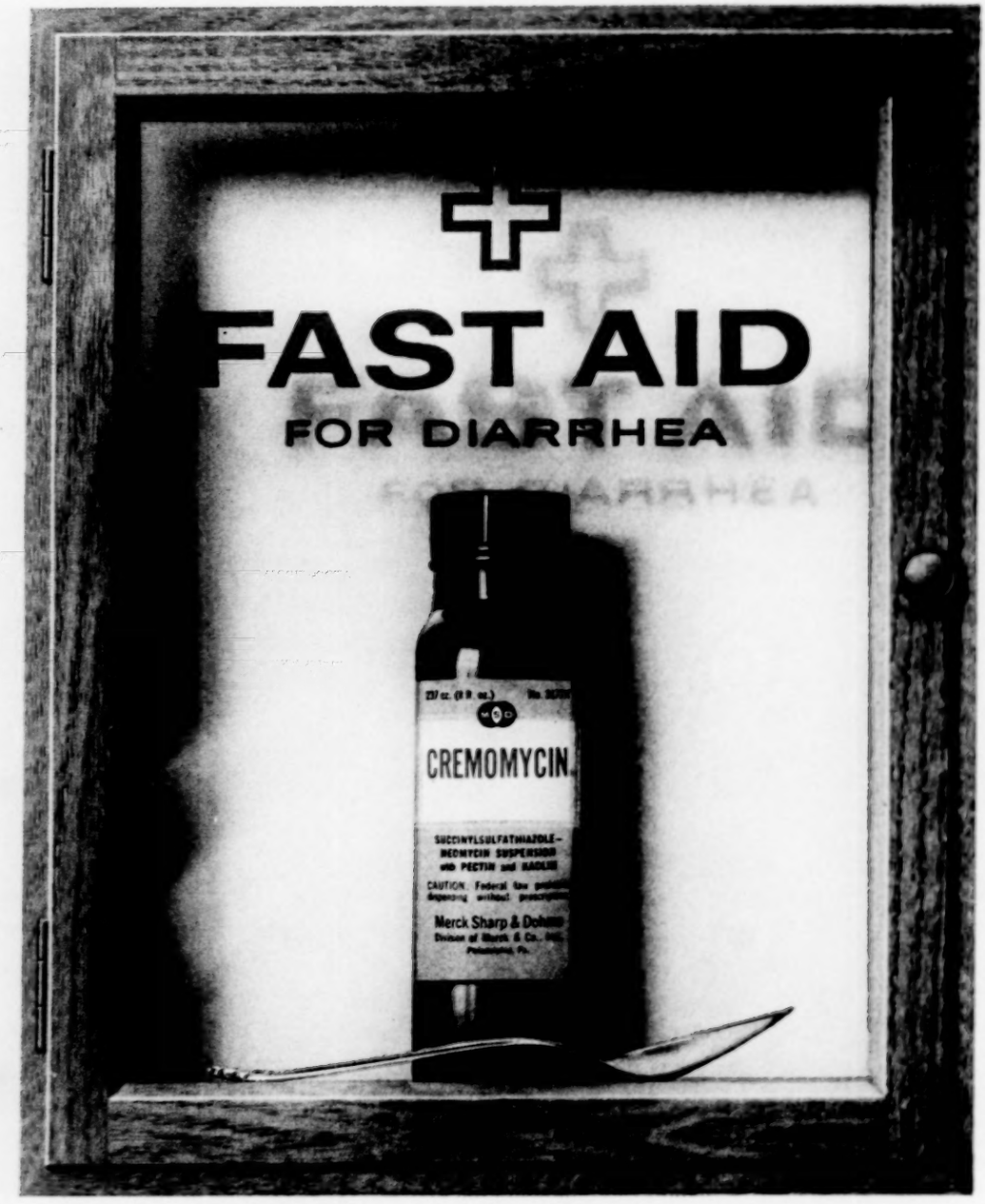
SYMPATHETIC LEVEL:
Bellergal relieves hot flashes, palpitations, tachycardia, tremor, sweats

PARASYMPATHETIC LEVEL:
Bellergal relieves nausea, hypersalivation, faintness

SANDOZ

BELLERGAL SPACETABS—Bellafoline 0.2 mg., ergotamine tartrate 0.6 mg., phenobarbital 40.0 mg. Warning: May be habit forming. (Color: Granular pattern of green, apricot and lemon yellow; compressed.)
Dosage: 1 in the morning, and 1 in the evening.

BELLERGAL TABLETS—Bellafoline 0.1 mg., ergotamine tartrate 0.3 mg., phenobarbital 20.0 mg. Warning: May be habit forming. (Color: Rose beige, sugar-coated.)
Dosage: 3 to 4 daily. In more resistant cases, dosage begins with 6 tablets daily and is slowly reduced.



Cremomycin® provides rapid relief of virtually all diarrheas

NEOMYCIN—actively bactericidal against a wide range of gram-negative intestinal pathogens, but relatively ineffective against certain diarrhea-causing organisms.

SULFASUXIDINE®, succinylsulfathiazole—an ideal adjunct to neomycin because it is highly effective against Clostridia and certain other neomycin-resistant organisms.

KAOLIN AND PECTIN—coat and soothe the inflamed mucosa, adsorb toxins, help provide rapid symptomatic relief.

Additional information on CREMOMYCIN is available to physicians on request.

MSD MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

a pair of cardiac patients:

both are free of pain—but only one is on

DILAUDID®

(Dihydromorphinone HCl)

swift, sure analgesia normally unmarred by nausea and vomiting

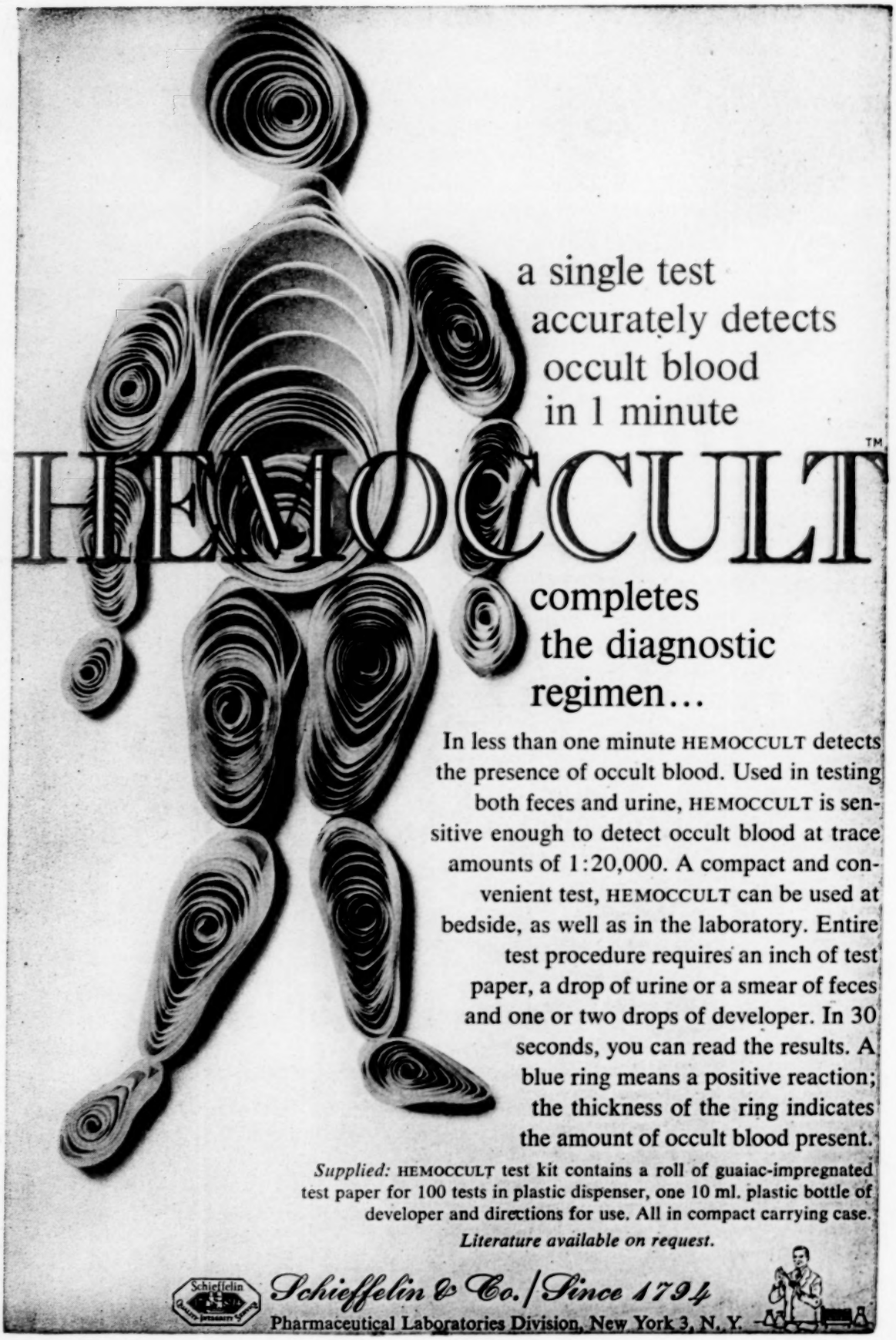
DILAUDID provides unexcelled analgesia in acute cardiovascular conditions. Onset of relief from pain is almost immediate. The high therapeutic ratio of DILAUDID is commonly reflected by lack of nausea and vomiting—and marked freedom from other side-effects such as dizziness and somnolence.

▲ **by mouth** ▲ **by needle** ▲ **by rectum**

2 mg., 3 mg., and 4 mg.

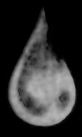
May be habit forming—usual precautions should be observed as with other opiate analgesics.

KNOLL PHARMACEUTICAL COMPANY • ORANGE, NEW JERSEY


a single test
accurately detects
occult blood
in 1 minute
HEMOCCULT™
completes
the diagnostic
regimen...
In less than one minute HEMOCCULT detects the presence of occult blood. Used in testing both feces and urine, HEMOCCULT is sensitive enough to detect occult blood at trace amounts of 1:20,000. A compact and convenient test, HEMOCCULT can be used at bedside, as well as in the laboratory. Entire test procedure requires an inch of test paper, a drop of urine or a smear of feces and one or two drops of developer. In 30 seconds, you can read the results. A blue ring means a positive reaction; the thickness of the ring indicates the amount of occult blood present.
Supplied: HEMOCCULT test kit contains a roll of guaiac-impregnated test paper for 100 tests in plastic dispenser, one 10 ml. plastic bottle of developer and directions for use. All in compact carrying case.
Literature available on request.
Schieffelin
Schieffelin & Co. / Since 1794
Pharmaceutical Laboratories Division, New York 3, N. Y.

aspirin buffered with the most widely-prescribed antacid...

Aspirin
300 mg
5 gr



MAALOX
150 mg

ASCRIPTIN

in long-term administration, as in Arthritis,
when aspirin combined with an antacid is desired:

Specify **Ascriptin**® RORER
the aspirin buffered with the best

To prevent or minimize gastric distress which often accompanies prolonged or high level administration of acetylsalicylic acid, ASCRIPTIN provides aspirin in combination with MAALOX®, the preferred professional antacid. The recognized superiority of MAALOX makes ASCRIPTIN a superior aspirin-antacid, with the virtues of buffered aspirin and with the added distinction of being promoted professionally only.

Indicated wherever salicylates are useful, ASCRIPTIN is particularly suited to the long-term requirements of your arthritic patients.

Supplied: Bottles of 100 and 500 tablets. For severe pain — Capsules ASCRIPTIN with Codeine (codeine phosphate 15 mg.), bottles of 50.

WILLIAM H. RORER, INC. PHILADELPHIA, PENNSYLVANIA

"R Day"

for the neuritis patient can be tomorrow

"R Day"—*when pain is relieved*—can come early for patients with inflammatory (non-traumatic) neuritis if treatment with Protamide is started promptly after onset.

Protamide is the therapy of choice for either early or delayed treatment, but early use assures greatest efficacy.

For example, in a 4-year study[1] and a 26-month study[2] a combined total of 374 neuritis patients treated with Protamide during the first week of symptoms responded as follows:

60% required only 1 or 2 daily injections for complete relief

96% experienced excellent or good results with 5 or less injections

Thus, the neuritis patient's first visit—especially an early one—affords the opportunity to speed his personal "R Day."

Protamide is available at pharmacies and supply houses in boxes of ten 1.3 cc. ampuls. Intramuscularly only, one ampul daily.

PROTAMIDE®

REFER TO PDR
PAGE 813

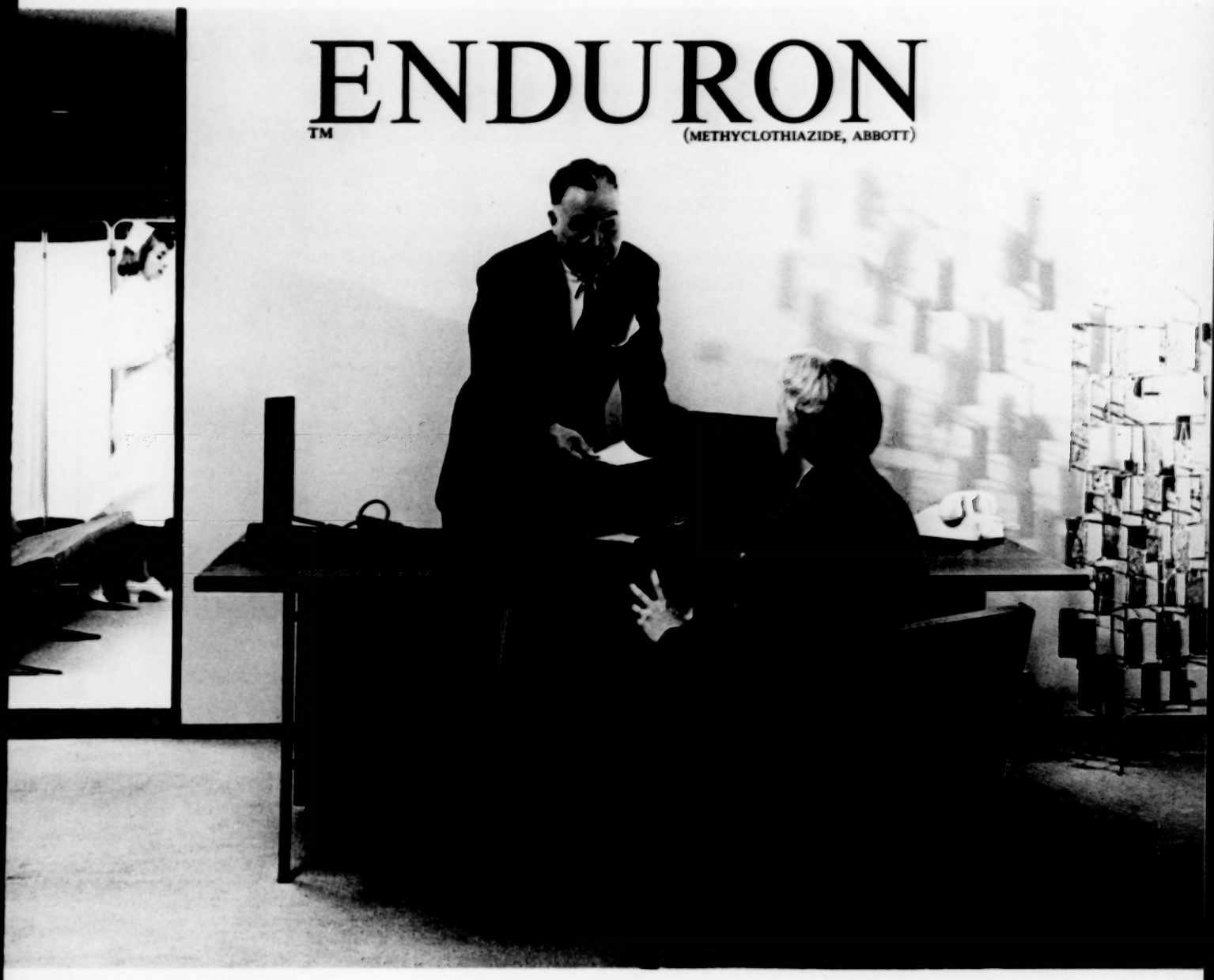
Sherman Laboratories
Detroit 11, Michigan

1. Lehrer, H. W., et al.: Northwest Med. 75:1249, 1955.
2. Smith, Richard T.: New York Med. 8:16, 1952.

The 24-hour diuretic-antihypertensive

ENDURON™

(METHYCLOTHIAZIDE, ABBOTT)



Nothing is simpler in thiazide therapy: Prescribe "Enduron once a day, every day"

One dose daily of this potent new thiazide is ample. It treats edema and hypertension around the clock. You can expect therapeutic action through the full 24 hour period (and longer).

What's more, Enduron provides an enhanced potassium-sparing effect. Whereas multiple dose drugs may cause multiple peaks of potassium loss, Enduron's single dose brings but a temporary single peak.

Enduron's once-a-day dosage is of course a convenience, too. Easy for the patient to remember. Easy for you to supervise. We invite you to experience its benefits . . . soon. *(See next page)*

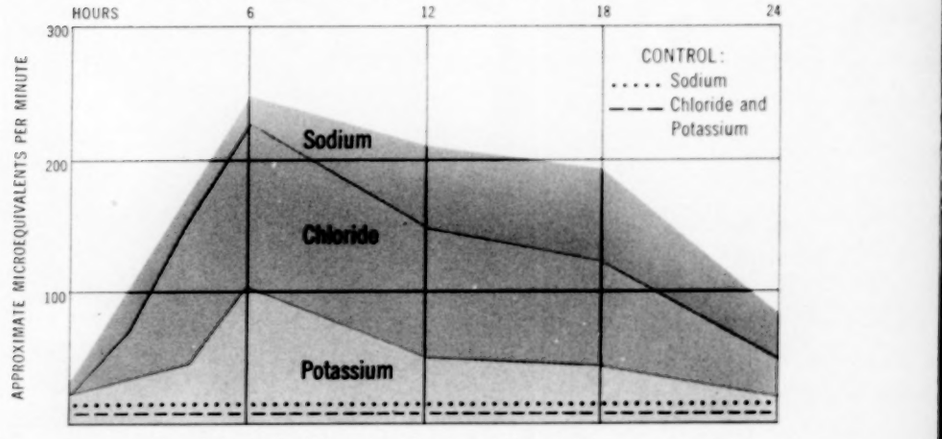
ABBOTT

1040.10A

Every ENDURON tablet delivers over 24 hours of continuous thiazide action

With this unique agent, you need just *one* daily dose to reduce edema and hypertension. Diuretic response reaches maximum in about six hours. It then follows a smooth, continuing plateau for most of the remaining day. Even at end of the 24 hours, you are still eliminating sodium well above control (i.e., undosed) amounts.

Usual Urinary Excretion Patterns Following 10 mg. of Enduron



Note that Enduron's effect on urinary potassium is minor: potassium depletion will seldom be a factor in your therapy. Similarly, Enduron's favorably high ratio of sodium versus chloride excretion means lessened likelihood of hypochloremic alkalosis.

How safe is Enduron?

Repeated oral doses of many thousand times the therapeutic amount, have been well tolerated in test animals for months. Since Enduron's milligram dosage in humans is low, it affords the security of an exceptionally safe therapeutic ratio.

Difficulty, if any, is apt to arise from therapy that's unnecessarily vigorous. Enduron is potent. 10 mg. produces at least as much sodium excretion as other available thiazides in *any* size dose. Single doses greater than 10 mg. don't accomplish greater diuresis, and aren't recommended or needed.

Prescribe the 24-hour diuretic-antihypertensive:

ENDURON

(METHYCLOTHIAZIDE, ABBOTT)

significant advance in thiazide therapy

ABBOTT

1. Ford, R. V., Current Therap. Res., 2:422-430, Sept., 1960.
2. Bryant, J. M., et. al., Current Therap. Res., 3:1-4, Jan., 1961.

1040108

NEW 8th EDITION

8 MODERN DRUG ENCYCLOPEDIA

and Therapeutic Index with monthly supplement MODERN DRUGS

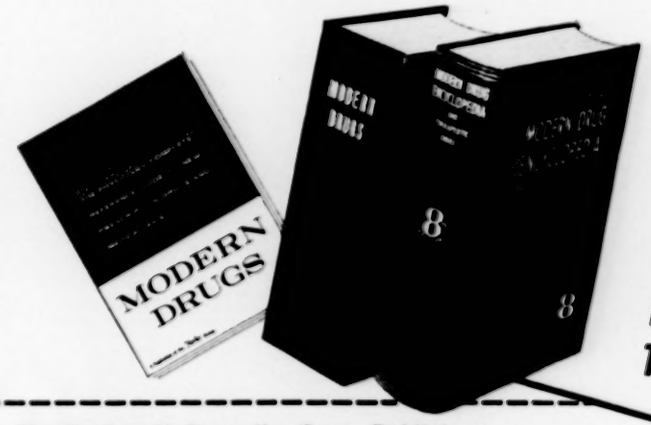
The only complete reference on new as well as established products.

Quickly answers questions about ethical pharmaceuticals.

MODERN DRUG ENCYCLOPEDIA, 8th Edition, an authoritative source of information on new and established pharmaceuticals. Gives you pertinent *facts* in concise form. Supplies facts you want to know to prescribe the new products with confidence. No struggle to keep cumbersome files up to date—just one compact bound volume and a compact binder for the monthly supplements.

MODERN DRUGS

A monthly supplement, with Robert S. Goodhart, M.D. as supervising editor, and John C. Helenore, Ph.G. as technical editor, supplies the same complete information on *new* pharmaceuticals as soon as they are available on your prescription. A convenient binder keeps the 24 issues together. Cumulative indices in *each* issue help you find *any* product listed in previous months.



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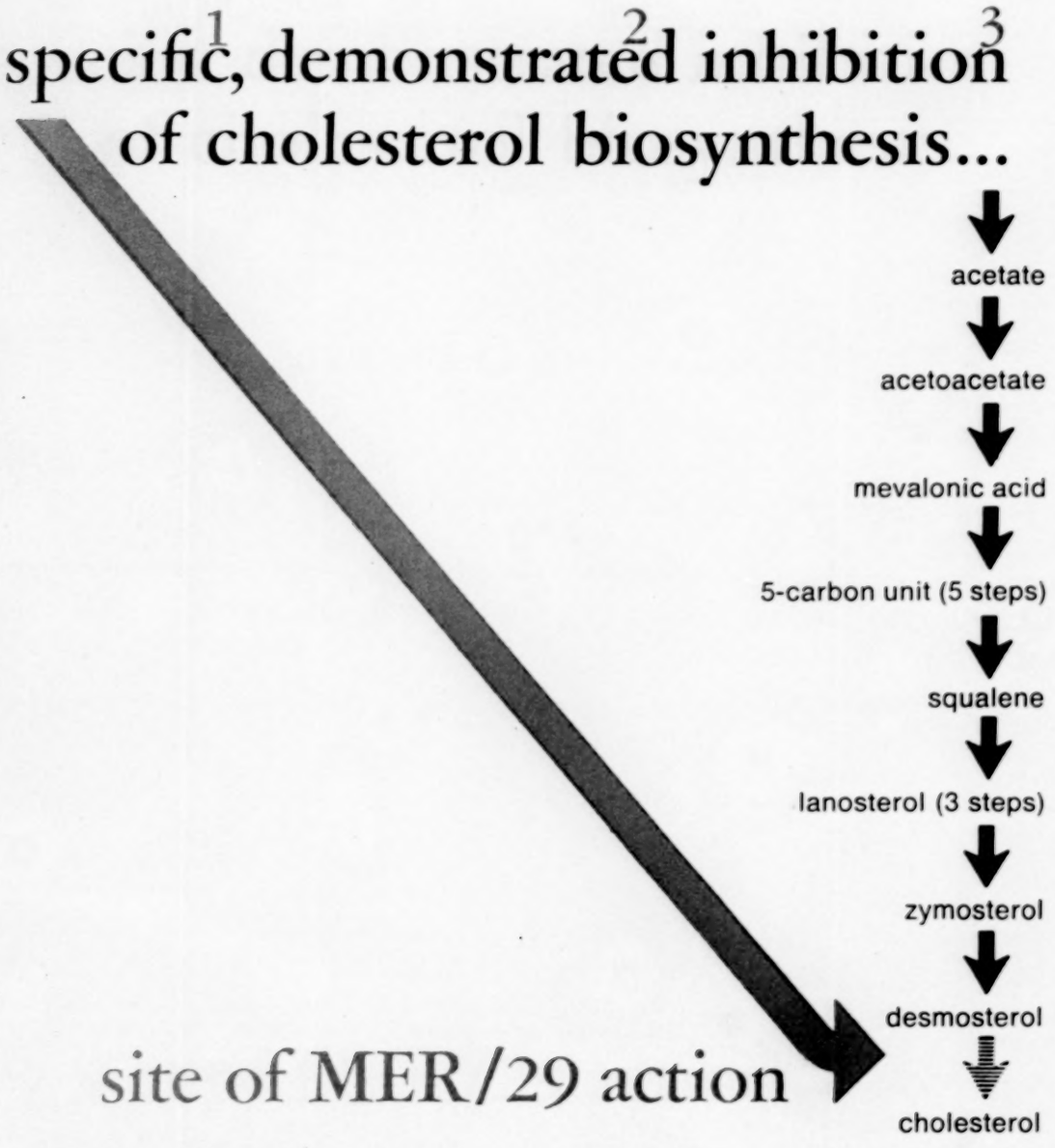
Please make checks payable to The Reuben H. Donnelley Corporation

*Includes 2-year supplementary service at $5.00 per year ($6.00 Foreign)

HOW MER/29 DIFFERS FROM OTHER CHOLESTEROL-LOWERING MEASURES



1. The primary, the *only* known action of MER/29 is to lower the total body pool of sterols (serum and tissue); no effect on any other system or organ reported to date.

2. "Using each patient as his own control, the peak *total* sterol radioactivity after injection of mevalonic acid-2-C^{14} was compared on and off MER/29. As much as a 50 per cent inhibition on MER/29 was observed in some patients."
—Steinberg, D.; Avigan, J., and Feigelson, E. B.: Circulation *22*:663 (Oct.) 1960.

3. "Studies of lipid metabolism have stressed the importance of cholesterol biosynthesis, as opposed to cholesterol intake, in determining cholesterol balance."
—National Heart Institute: Diet, Hormones, and Atherosclerosis..., Bethesda, Md., U.S. National Institutes of Health, 1958.

...leading to specific, demonstrated advantages in cholesterol-lowering therapy

particularly in patients with coronary artery disease, generalized atherosclerosis, and other conditions thought to be associated with abnormal cholesterol metabolism

MER/29 REDUCES CHOLESTEROL IN AS MANY AS 8 OUT OF 10 PATIENTS: MER/29 reduces both serum and tissue cholesterol without strict adherence to diet. Although some physicians prefer to use MER/29 in conjunction with controlled diets, cholesterol can be reduced successfully without such limitation.

CONCURRENT BENEFITS REPORTED IN SOME PATIENTS: In patients with coronary artery disease, some of the concurrent benefits reported include decreased incidence and severity of anginal attacks, improved ECG patterns, diminished nitroglycerin dependence, and increased sense of well-being.

MER/29 HAS PRODUCED FEW SIDE EFFECTS, NO TOXICITY: Patients have been treated with MER/29 for continuous periods up to 19 months. In no case has there been evidence of serious toxic effects on the function of any vital organ or system. Side effects (nausea, headache, dermatitis) are rare and have usually been associated with dosages greater than those recommended for effective therapy.

MER/29 is compatible with other cardiovascular therapies. It can be used along with measures which control anxiety, hypertension, obesity and other conditions associated with cardiovascular disorders. These include nitroglycerin, PETN, and anticoagulants.

CAUTION: Since long-term MER/29 therapy may be necessary, periodic examinations, including liver function tests, are desirable. Also, since MER/29 inhibits cholesterol biosynthesis, and cholesterol plays an important role in the development of the fetus, the drug is *contraindicated in pregnancy.*

DOSAGE: One 250 mg. capsule daily, before breakfast.

SUPPLIED: Bottles of 30 pearl gray capsules.
Complete bibliography and product information available on request.

MER/29

(triparanol)

Merrell

The Wm. S. Merrell Company
Division of Richardson-Merrell Inc.
Cincinnati, Ohio • Weston, Ontario

Trademark: MER/29®

extends the usefulness of Vitamin K_1 therapy†...

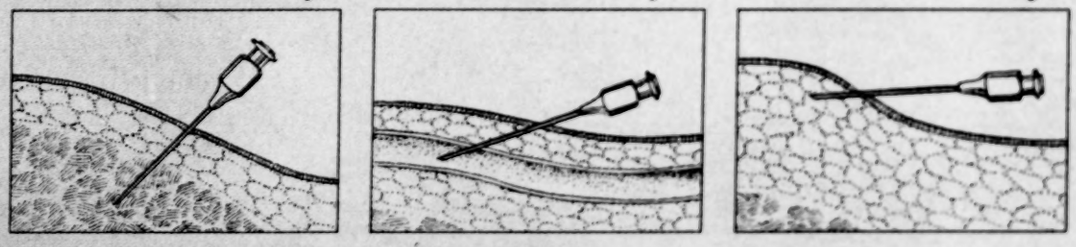
NEW Injection

Aqua

AQUEOUS COLLOIDAL SOLUTION

†a clear, stable, aqueous colloidal solution for administration

• intramuscularly • intravenously • subcutaneously



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*Council on Drugs: New and Nonofficial Drugs, Philadelphia, J. B. Lippincott Co., 1960, p. 732

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Erythropoietin—a significant discovery in clinical hematology

A wealth of evidence now confirms the fact that red blood cell production is controlled by the hormone erythropoietin.[1-3] Demonstrated in human plasma,[4] erythropoietin has been shown to produce reticulocytosis,[1,5-7] increase utilization of the Fe^{59} isotope, and increase erythrocyte precursors in marrow cultures.[3,8]

ERYTHROPOIETIN FOUND TO CONTROL RED CELL FORMATION

erythropoietin levels—new criteria in diagnosis of anemia—Increased erythropoietin blood levels can be demonstrated in severe anemia and following the start of accelerated formation.[9] Soon thereafter, the effect of the higher levels appears as an increased erythroid marrow activity.[10] Since the hemopoietic marrow is capable of producing more red cells than normally required, many anemias may be due to inadequate erythropoietin levels—a result of subnormal production or excessive excretion.

how does erythropoietin affect iron metabolism? Absorption and utilization of iron are dependent upon the rate of bone marrow erythropoiesis which, in turn, is dependent upon erythropoietin levels.[11,12] Thus, the demand for iron created by accelerated erythropoiesis is satisfied by both increased gastrointestinal absorption and mobilization of storage iron. Inadequate erythropoietin levels would seemingly account for the frequently disappointing results with the use of iron alone in many of the anemias.

can medication increase erythropoietin levels? Cobalt has been shown to be strikingly effective in increasing the production of erythropoietin.[13,14] Cobalt-enhanced erythropoietin accelerates red cell production and improves iron utilization with a subsequent increase in hemoglobin and erythrocytes. The new concepts of the cause, diagnosis, and management of anemia may now be applied clinically on the sound basis of extensive studies published on RONCOVITE®—MF, the therapeutic cobalt-iron hematinic.

(1) Gordon, A. S.: Physiol. Rev. **39**:1, 1959. (2) Erslev, A. J.: J. Lab. & Clin. Med. **50**:543, 1957. (3) Rosse, W. F., and Gurney, C. W.: J. Lab. & Clin. Med. **53**:446, 1959. (4) Gurney, C. W., Goldwasser, E., and Pan, C.: J. Lab. & Clin. Med. **50**:534, 1957. (5) Rambach, W. A.; Alt, H. F., and Cooper, J. A. D.: Blood **12**:1101, 1957. (6) Gordon, A. S., **et al.**: Proc. Soc. Exp. Biol. & Med. **92**:598, 1956. (7) Erslev, A. J.: Blood **10**:954, 1955. (8) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L. F.: Blood **13**:55, 1958. (9) Stohlman, F., Jr., and Brecher, G.: Proc. Soc. Exp. Biol. & Med. **100**:40, 1959. (10) Kraus, L. M., and Kraus, A. P.: Fed. Proc. **18**:1051, 1959. (11) Bothwell, T. H.; Pirzio-Biroli, G., and Finch, C. A.: J. Lab. & Clin. Med. **51**:24, 1958. (12) Beutler, E., and Buttenwieser, E.: J. Lab. & Clin. Med. **55**:274, 1960. (13) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L.: Science **125**:1085, 1957. (14) Murdock, H. R., Jr., and Klotz, L. J.: J. Am. Pharm. A. (Scient. Ed.) **48**:143, 1959.

For a complete background file on erythropoietin, please write to the Medical Service Department of:

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Bibliography: 1. Kestler, O. C.: *J.A.M.A.* *171*:2039 (April 30) 1960.

Complete information on RELA including indications, dosage, side effects, and precautions is available to physicians on request.

M-365 JANUARY 1961

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Description	Upjohn brand of medroxyprogesterone acetate.	Aqueous suspension, 50 mg. Provera per cc., for intramuscular injection only.
Indications	Threatened and habitual abortion, infertility, dysmenorrhea, secondary amenorrhea, premenstrual tension, functional uterine bleeding.	Threatened and habitual abortion, endometriosis.
Dosage Threatened abortion	10 to 30 mg. daily until acute symptoms subside.	50 mg. I. M. daily while symptoms are present, followed by 5.0 mg. weekly through 1st trimester, or until fetal viability is evident.
Habitual abortion		
1st trim.	10 mg. daily.	50 mg. I.M. weekly.
2nd trim.	20 mg. daily.	100 mg. I.M. q. 2 wks.
3rd trim.	40 mg. daily, through 8th month.	100 mg. I.M. q. 2 wks. through 8th month.
Supplied:	2.5 mg. scored, pink tablets, bottles of 25; 10 mg. scored, white tablets, bottles of 25 and 100.	Sterile aqueous suspension for intramuscular use only, 50 mg. per cc., in 1 cc. and 5 cc. vials.†

Precautions: Clinically, Provera is well tolerated. No significant untoward effects have been reported. Animal studies show that Provera possesses adrenocorticoid-like activity. While such adrenocorticoid action has not been observed in human subjects, patients receiving large doses of Provera continuously for prolonged periods should be observed closely. Likewise, large doses of Provera have been found to produce some instances of female fetal masculinization in animals. Although this has not occurred in human beings, the possibility of such an effect, particularly with large doses over a long period of time, should be considered.

Provera, administered alone or in combination with estrogens, should not be employed in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital malignancy has been eliminated.

†Each cc. of Depo-Provera contains: Medroxyprogesterone acetate, 50 mg.; Polyethylene glycol 4000, 28.8 mg.; Polysorbate 80, 1.92 mg.; Sodium chloride, 8.65 mg.; Methylparaben, 1.73 mg.; Propylparaben, 0.19 mg.; Water for injection, q.s.

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April, 1961

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*Bickerman, H. A., et al.: Physiologic and steroid therapy in respiratory disease, Scientific Exhibit, A.M.A. Convention, Atlantic City, N. J., June 8-12, 1959.

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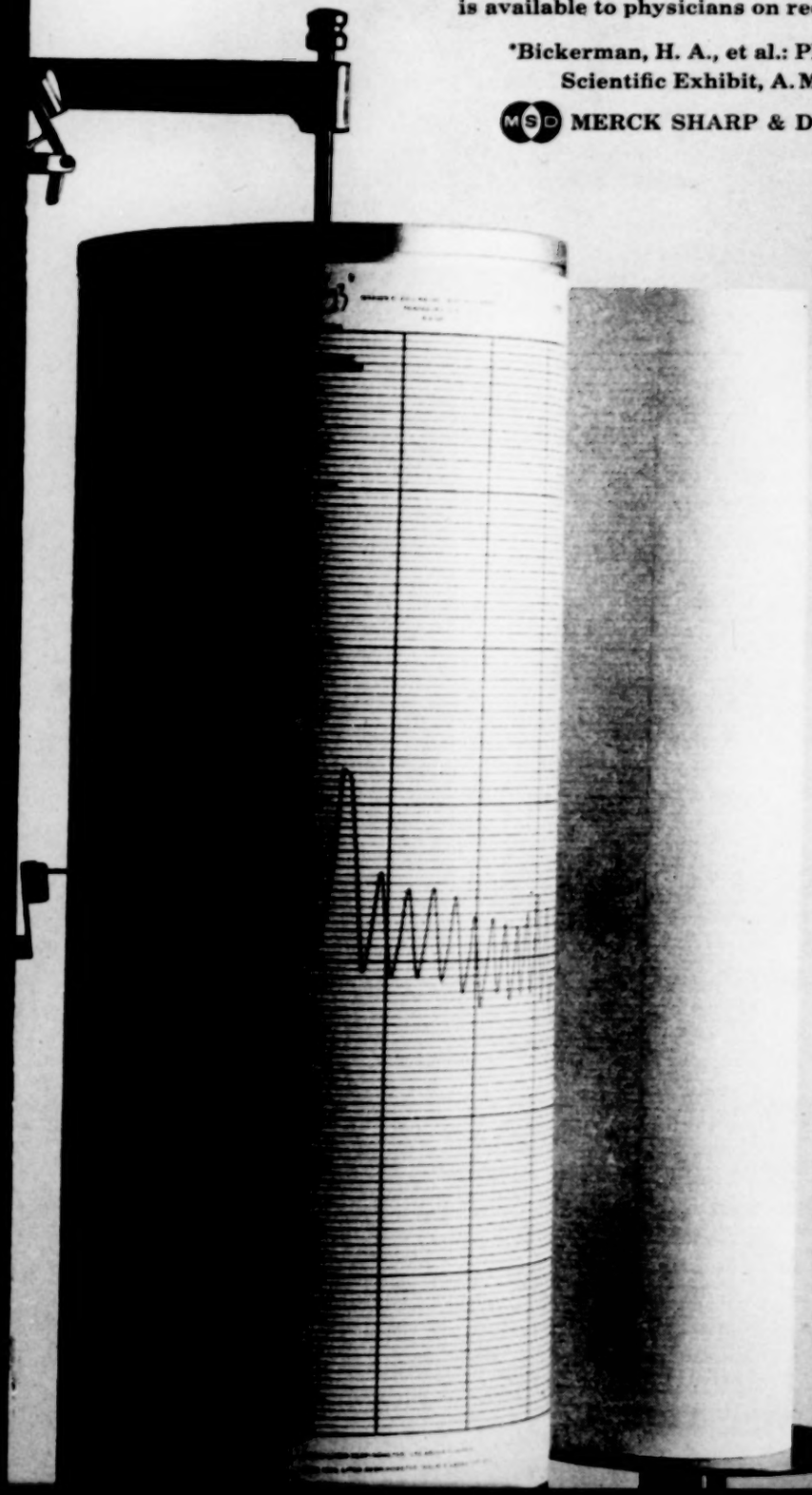

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Dexamethasone
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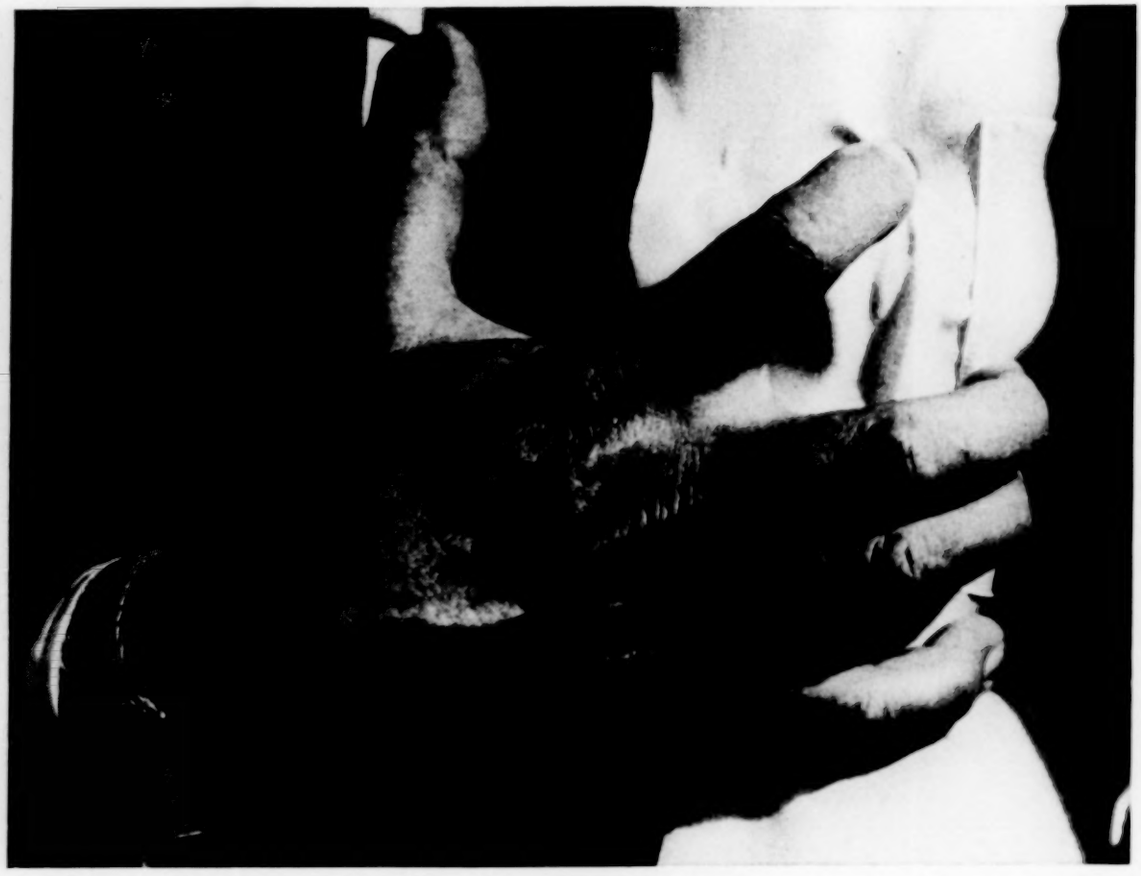

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REFERENCES: **1.** Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Pelner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

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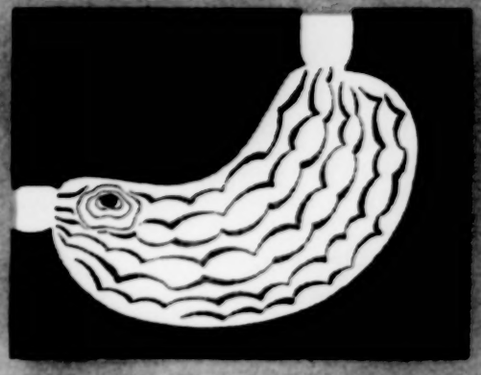

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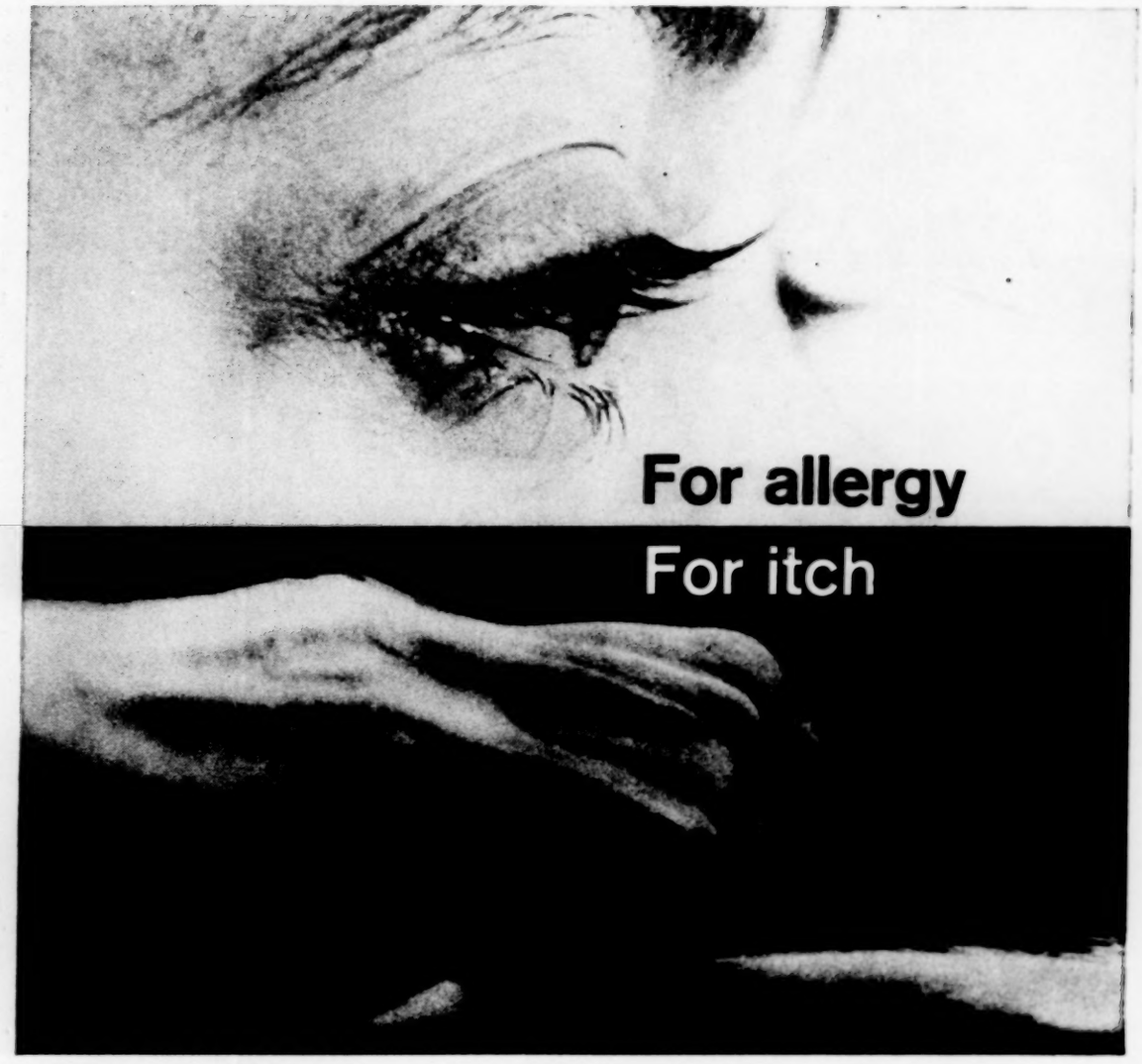

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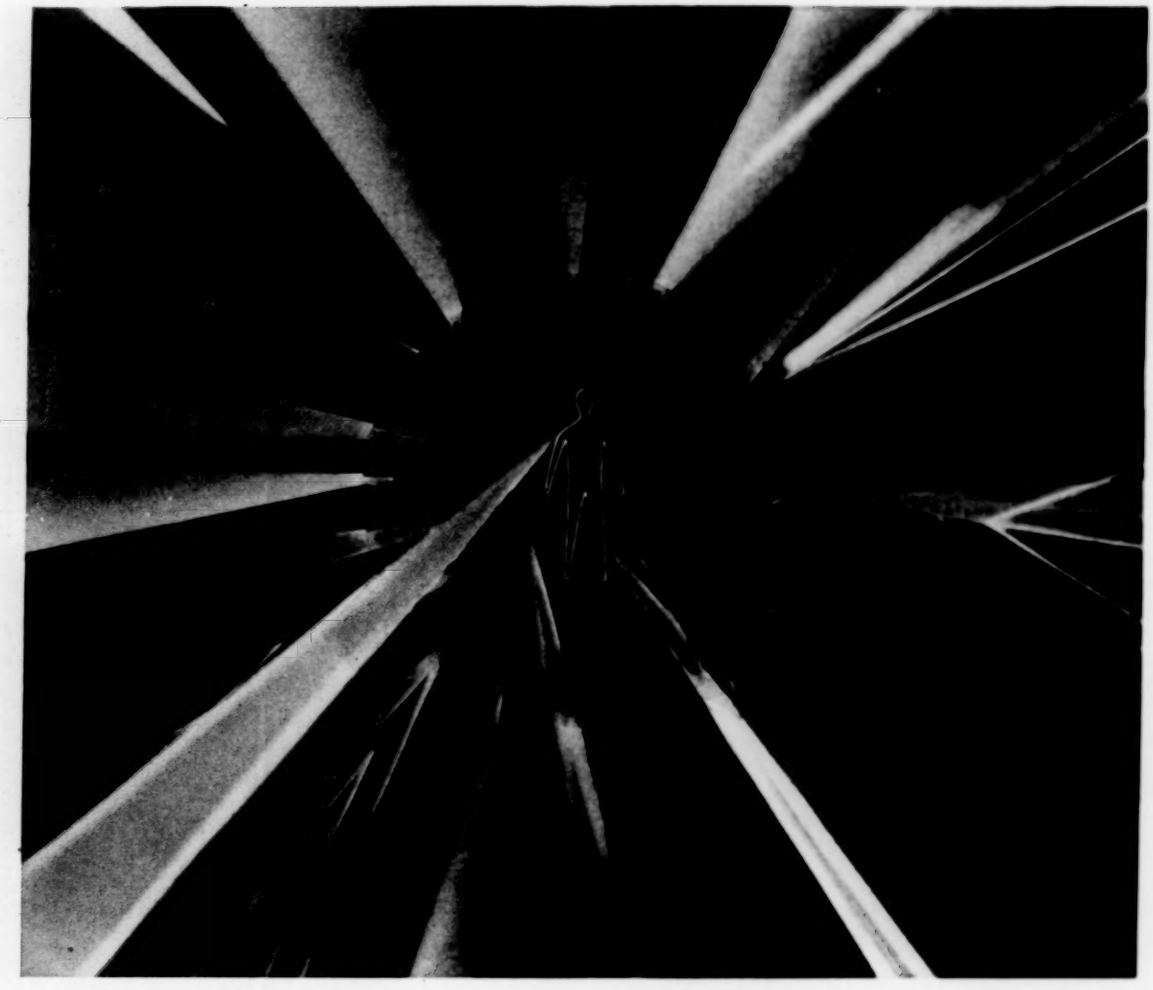

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The American Journal of Medicine

Vol. XXX MAY 1961 No. 5

CONTENTS

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Contents continued on page 5

CONTENTS continued – May 1961

VOLUME THIRTY NUMBER FIVE

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VOLUME THIRTY NUMBER FIVE

ERRATUM

Two typographical errors occurred in the article entitled "Reversal of Diurnal Rhythm in Excretion of Water and Salt in Primary Hyperaldosteronism," by E. J. Lennon et al. *Am. J. Med.*, 30: 475, 1961. Although the units in the figures were labelled correctly, the text on page 480, paragraph 2, reads "2,690 mEq./minute," and later "1,420 mEq./minute." In both instances, *microequivalents* is the correct term. The same error occurs on page 482, paragraph 2, where "620 mEq./minute" is written instead of "620 μEq./minute."

Advertisers' Index on Pages 107 and 108

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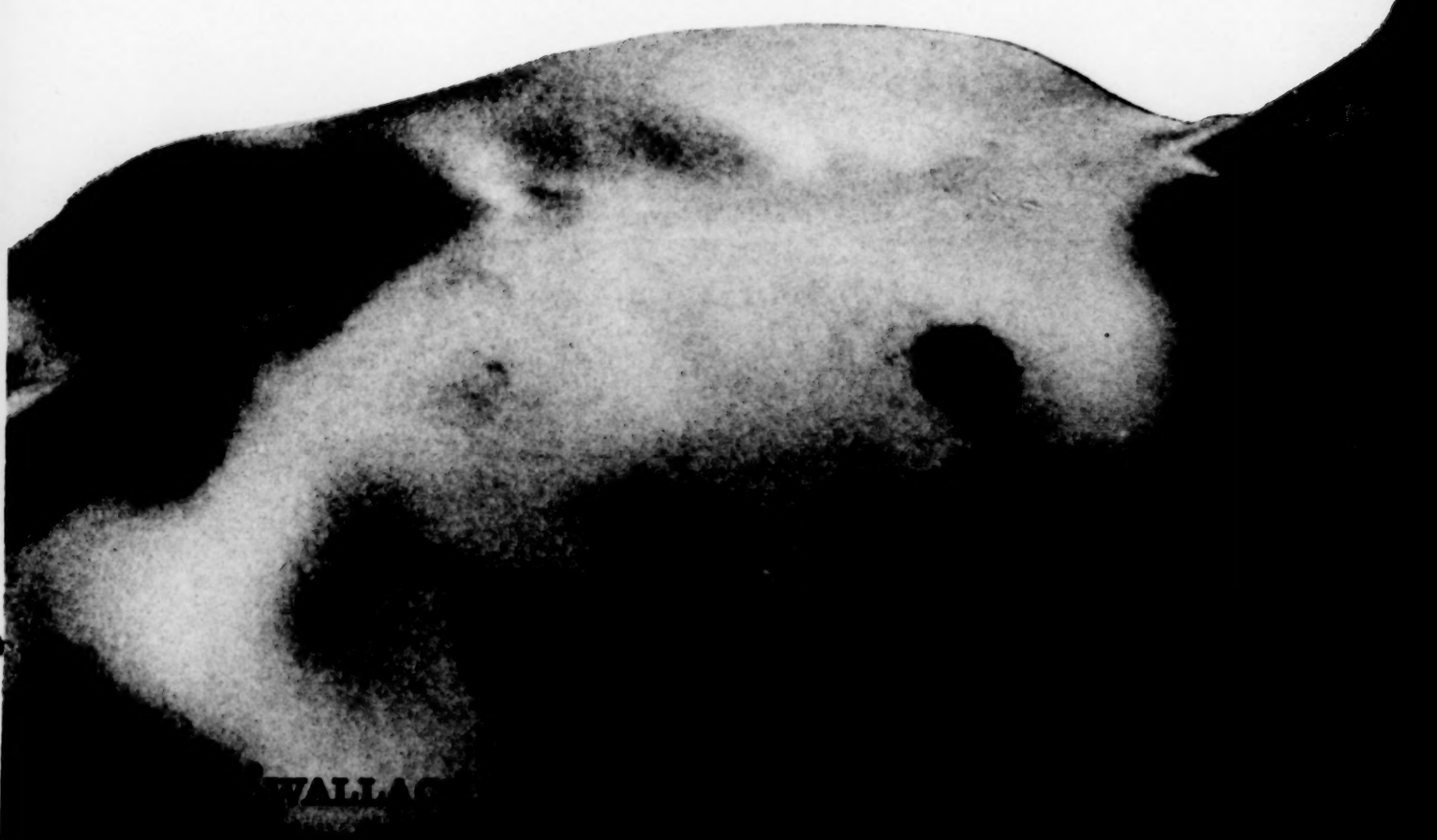

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- vertigo
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pollenosis	3 to 4 tablets	1 day	decrease dosage daily by 1 tablet until symptoms recur, then adjust to satisfactory level	usually 10 to 14 days
allergic or inflammatory dermatoses	4 to 8 tablets	until control	reduce dosage by ½ to 1 tablet every 2 or 3 days to satisfactory level	as required
allergic or inflammatory eye disorders	4 to 8 tablets	until control or up to 7 days	reduce dosage by 1 tablet daily to satisfactory level	as required

*After initial control is established, dosage should be reduced gradually to a maintenance level.

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For complete details, consult latest Schering literature available from your Schering Representative or Medical Services Department, Schering Corporation, Bloomfield, New Jersey.

Bibliography: 1. Goldman, L.: Investigation of a New Steroid in Dermatology. Paper presented at First Conference on the Clinical Application of Betamethasone: A New Corticosteroid, New York City, May 8, 1961. 2. Nierman, M. M.: The Use of Betamethasone in Dermatology. *Ibid.* 3. Gant, J. Q., and Gould, A. H.: Betamethasone: A Clinical Study. *Ibid.* 4. Frank, L.: The Place of Betamethasone in Dermatologic Practice. *Ibid.* 5. Hampton, S. F.: Betamethasone—A New Steroid in Allergy: A Preliminary Report. *Ibid.* 6. Bukantz, S. C.: Observations on the Use of Betamethasone in the Intractable Asthmatic Child. *Ibid.* 7. Bedell, H.: A New Systemic Steroid in the Treatment of Allergies in Office Practice. *Ibid.* 8. Schwartz, E.: Clinical Evaluation of Betamethasone in Chronic Intractable Bronchial Asthma. *Ibid.* 9. Kammerer, W. H.: Observations on the Effects of Betamethasone in Rheumatoid Arthritis. *Ibid.* 10. Cohen, A., and Goldman, J.: Management of Rheumatoid Arthritis with a New Steroid. *Ibid.* 11. Gordon, D. M.: Betamethasone—A New Corticosteroid in Ophthalmology. *Ibid.* 12. Abrahamson, I. A., Jr.: A Clinical Evaluation of Betamethasone. *Ibid.*

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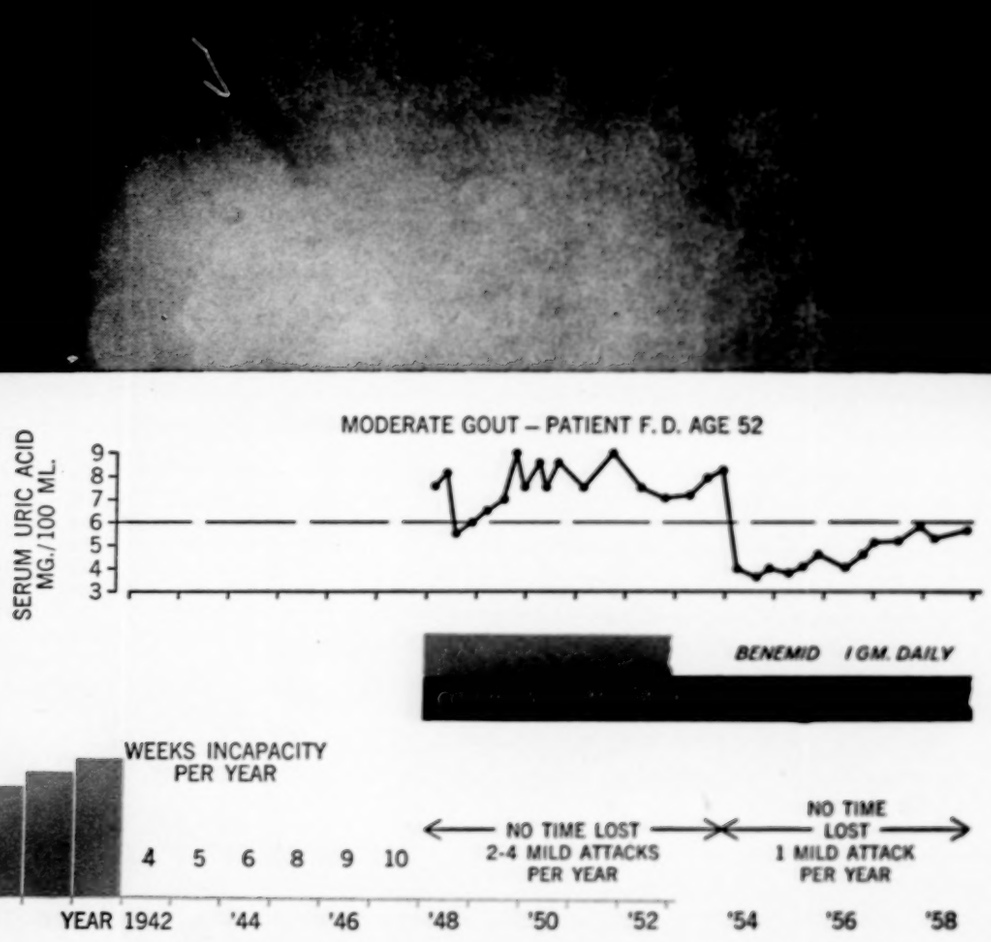
to
improve

In Brief Niamid, brand of nialamide, is 1-(2-[benzylcarbamyl] ethyl)-2-isonicotinyl-hydrazine, a well-tolerated antidepressant that may correct or relieve depression on once-a-day dosage. **Indications:** Depressive syndromes of varying degrees of severity may be responsive to Niamid including: involutional melancholia, postpartum depression, depressed phase of manic-depressive reaction, senile depression, reactive depression, schizophrenic reaction with depressive component, psychoneurotic depression. ■ In neurotic or psychotic patients, Niamid may normalize or favorably modify aberrant or excessive reactions and symptoms of depression such as: phobias, guilt feelings, dejection, feeling of inadequacy, discouragement, worry, uneasiness, distrustfulness, hypochondriacal and nihilistic ideas, difficulty in concentration, insomnia, loss of energy or drive, indecision, hopelessness, helplessness, decreased functional activity, emotional and physical fatigue, irritableness, inability to rest or relax, sadness, anorexia and weight loss, and withdrawal from society. *In the withdrawn patient,* Niamid may elevate the mood so that there is increased activity, increased awareness and interest in surroundings, and increased participation in group activities. Appetite may be increased and there may be decreased fatigability. Lack of clinical response to other antidepressant therapy does not preclude a favorable response to Niamid. Relief of depression may also be evidenced by elimination or reduction of the need for somatic therapy, such as electroshock. *In patients suffering from depression associated with chronic illness,* Niamid may improve mental outlook, reduce the impact of pain, decrease the amounts of narcotics or analgesics needed, and improve appetite and well-being. *In patients with angina pectoris,* Niamid has been found to be a useful adjunct to management through reduction in frequency of attacks and pain. **Dosage:** Starting dosage is 75 to 100 mg. on a once-a-day or divided daily basis. This may subsequently be adjusted depending upon the tolerance and response. Responses to Niamid are not usually rapid, and revisions of dose should be withheld until at least a few days have elapsed at each level. Increments or decrements of 12½-25 mg. are generally sufficient. A daily dosage of 200 mg. is the maximum recommended for routine use. (As much as 450 mg. daily has been used in some patients.) **Side Effects:** Niamid, in clinical use, has been characterized by a significant lack of toxicity. It is generally well tolerated. Nervousness, restlessness, insomnia, hypomania, or mania, sometimes occur. Occasional headache, weakness, lethargy, vertigo, dryness of the mouth, blurred vision, increased perspiration, constipation, mild skin rash, mild leukopenia, and epigastric distress may be obviated or modified by reductions in dose. Effects due to monoamine oxidase inhibition persist for a substantial period following discontinuation of the drug. **Precautions and Contraindications:** Hepatic toxicity has not been reported in extensive clinical studies. However, if previous or concurrent liver disease is suspected, the possibility of hepatic reactions and liver function studies should be considered. ■ The suicidal patient is always in danger, and great care must be exercised to maintain all security precautions. The apathetic patient may obtain sufficient energy to harm himself before his depression has been fully alleviated. ■ Niamid may potentiate sedatives, narcotics, hypnotics, analgesics, muscle relaxants, sympathomimetic agents, thiazide compounds and stimulants, including alcohol. Caution should be exercised when rauwolfia compounds and Niamid are administered simultaneously. Rare instances have been reported of reactions (including atropine-like effects, and muscular rigidity) occurring when imipramine was administered during or shortly after treatment with certain other drugs that inhibit monoamine oxidase. **In Cardiology:** The central effects of Niamid may encourage hyperactivity and the patient should be closely observed for any such manifestation. Orthostatic hypotension or hypertensive episodes occur in a few individuals; cardiac patients should be carefully selected and closely supervised. **In Epilepsy:** Although in some patients therapeutic benefits have been achieved with Niamid, in others the disease has been aggravated. Care should be exercised in the concomitant use of imipramine, since such treatment with monoamine oxidase inhibitors has been reported to aggravate the grand mal seizures. **In Tuberculosis:** Existing data do not indicate whether resistance of M. tuberculosis to isoniazid may be induced with Niamid therapy; nevertheless, it should be withheld in the depressed patient with coexisting tuberculosis who may need isoniazid. ■ As with all therapeutic agents excreted in part via the kidney, due caution in adjusting dosage in patients with impaired renal function should be observed. **Supplied:** Niamid (Nialamide) Tablets, 25 mg.: 100's—pink, scored tablets; 100 mg.: 100's—orange, scored tablets./*More detailed professional information available on request.*

Before treatment.
Extensive gouty changes in base of proximal phalanx of great toe and in head and shaft of the first metatarsal.



Effect of colchicine and BENEMID on serum uric acid level and periods of incapacity.[2]

NEW

for optimal management of gout

a complementary formulation of two classic anti-gout agents

"Prophylactic management [of gout] embodies the use of the two agents just discussed, namely, colchicine and Benemid. Each one complements the other. Neither one by itself is as effective as a combination....Since 1950, Benemid has been available and the greater the experience we have with the combination of colchicine and Benemid the greater the reliance we place upon these two drugs."[3]

Composition: Each tablet contains 0.5 mg. colchicine and 0.5 Gm. BENEMID probenecid.

Dosage between acute episodes: Mild, 1 tablet a day; moderate, 1 tablet twice daily; severe, 1 tablet three or more times daily.

Supply: Bottles of 100.

1. Talbott, J. H.: Gout, New York, Grune & Stratton, 1957, pp. 162, 163. 2. Talbott, J. H.: Gouty arthritis, Minn. Med. *42*:1044, Aug. 1959. 3. Talbott, J. H.: Recognition and treatment of gouty arthritis, Current Medical Digest *26*:57, Nov. 1959.

Also available: *BENEMID probenecid, 0.5 Gm. tablets, bottles of 100.*

For additional information,
write Professional Services,
Merck Sharp & Dohme, West Point, Pa.

MSD

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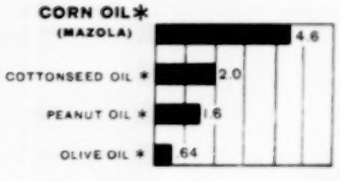
of vegetable oils...

Mazola® liquid corn oil is best for replacing saturated fats

because Mazola is both unexcelled in polyunsaturates (that reduce serum cholesterol) and lowest in saturates (that raise serum cholesterol).

HERE'S PROOF:
This chart shows that the ratio of polyunsaturates to saturates provided by Mazola Corn Oil is more than twice that of any other leading vegetable oil.



*U. S. Dept. of Agriculture Reports—1959

COMPOSITION OF MAZOLA CORN OIL
Mazola Corn Oil has the following average composition:

Fatty Acids	Grams/ 100 grams	Grams/ fl. oz. (2 tablespoons)
Polyunsaturates...	52-58	14-15.7
Monounsaturates..	28-36	7.5-9.7
Saturates	10-14	2.8-3.8
Natural Sitosterols...	1 (0.9-1.3)	0.14
Natural Tocopherols..	about 0.1	0.015
Cholesterol	none	none
Salt (Sodium chloride)	none	none

Calories—125/tablespoon
Iodine value—124 average

CORN OIL CONTINUES TO BE A PREFERRED VEGETABLE OIL IN NUTRITIONAL STUDIES OF HYPERCHOLESTEROLEMIA.

Your patients will find Mazola Corn Oil ideally suited for salad dressings, baking and frying. By instructing them to use Mazola in place of a substantial portion of more saturated types of fat, and to watch their caloric intake, you frequently will be able to lower the serum cholesterol with minimum changes in eating habits.

MAZOLA CORN OIL IS ALSO AVAILABLE IN CANADA, WESTERN EUROPE, LATIN AMERICA AND MANY OTHER COUNTRIES THROUGHOUT THE WORLD

FREE!
Valuable aid for guiding your hypercholesterolemic patient in dietary control: **A Pad of Menu Guides** based on 2,000 calories per day, with which you may readily construct a diet pattern best suited to your patient's needs.

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The 24-hour diuretic-antihypertensive

ENDURON™

(METHYCLOTHIAZIDE, ABBOTT)

Nothing is simpler in thiazide therapy: Prescribe "Enduron once a day, every day"

One dose daily of this potent new thiazide is ample. It treats edema and hypertension around the clock. You can expect therapeutic action through the full 24 hour period (and longer).

What's more, Enduron provides an enhanced potassium-sparing effect. Whereas multiple dose drugs may cause multiple peaks of potassium loss, Enduron's single dose brings but a temporary single peak.

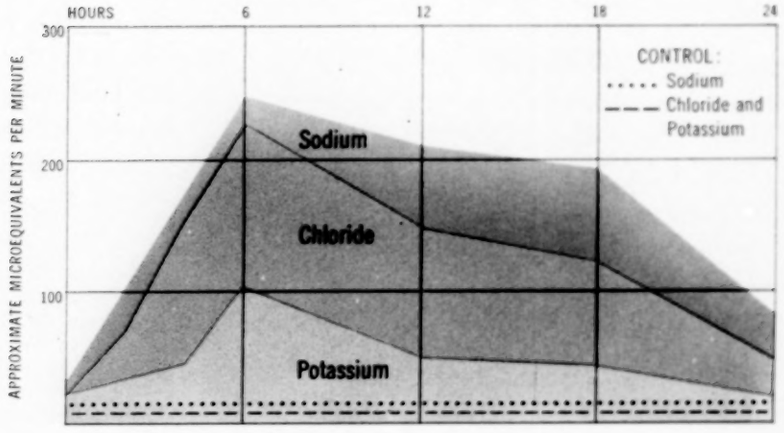
Enduron's once-a-day dosage is of course a convenience, too. Easy for the patient to remember. Easy for you to supervise. We invite you to experience its benefits . . . soon. *(See next page)*

ABBOTT

Every ENDURON tablet delivers over 24 hours of continuous thiazide action

With this unique agent, you need just *one* daily dose to reduce edema and hypertension. Diuretic response reaches maximum in about six hours. It then follows a smooth, continuing plateau for most of the remaining day. Even at end of the 24 hours, you are still eliminating sodium well above control (i.e., undosed) amounts.

Usual Urinary Excretion Patterns Following 10 mg. of Enduron



Note that Enduron's effect on urinary potassium is minor; potassium depletion will seldom be a factor in your therapy. Similarly, Enduron's favorably high ratio of sodium versus chloride excretion means lessened likelihood of hypochloremic alkalosis.

How safe is Enduron?

Repeated oral doses of many thousand times the therapeutic amount, have been well tolerated in test animals for months. Since Enduron's milligram dosage in humans is low, it affords the security of an exceptionally safe therapeutic ratio.

Difficulty, if any, is apt to arise from therapy that's unnecessarily vigorous. Enduron is potent. 10 mg. produces at least as much sodium excretion as other available thiazides in *any* size dose. Single doses greater than 10 mg. don't accomplish greater diuresis, and aren't recommended or needed.

Prescribe the 24-hour diuretic-antihypertensive:

ENDURON

(METHYCLOTHIAZIDE, ABBOTT)

significant advance in thiazide therapy

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1. Ford, R. V., Current Therap. Res., 2:422-430, Sept., 1960.
2. Bryant, J. M., et. al., Current Therap. Res., 3:1-4, Jan., 1961.

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to combat the three-pronged assault of urinary tract infections — *bacteriuria — tissue infection — discomfort*

UROBIOTIC®

COSA-TERRAMYCIN® — SULFONAMIDE — ANALGESIC

Only UROBIOTIC *contains:* OXYTETRACYCLINE (with glucosamine for enhanced absorption) — notable for its wide tissue distribution, high urinary concentration, excellent toleration and proven antibiotic effectiveness against even so troublesome an invader as *Pseudomonas;* SULFAMETHIZOLE — an unusually soluble, highly active sulfonamide; PHENYLAZO-DIAMINO-PYRIDINE — for effective local analgesia.

IN BRIEF

INGREDIENTS: Each Urobiotic capsule contains 125 mg. Terramycin® (oxytetracycline) with 125 mg. glucosamine HCl, 250 mg. sulfamethizole, and 50 mg. phenylazo-diamino-pyridine HCl.

INDICATIONS: Urobiotic is indicated in the treatment of a number of common genitourinary infections caused by susceptible organisms. It may also be used prophylactically before and after genitourinary or pelvic surgery, following instrumentation procedures, during the use of retention catheters, and in patients with conditions such as cord bladder or cystocele.

DOSAGE: In adults, a dose of 1 or 2 capsules four times daily is suggested, depending upon the severity and response of the infection. In children 60 to 100 lbs., the suggested average dose is 1 capsule four times daily; in children under 60 lbs., 1 capsule three times daily. Therapy should be continued for a minimum of 7 days or until bacteriologic cure is effected in acute urinary tract infections.

CONTRAINDICATIONS: Urobiotic may be contraindicated in patients with chronic glomerulonephritis, hepatitis, hepatic failure, uremia, and obstructive lesions of the urinary tract, and should not be used in patients sensitive to any of its components.

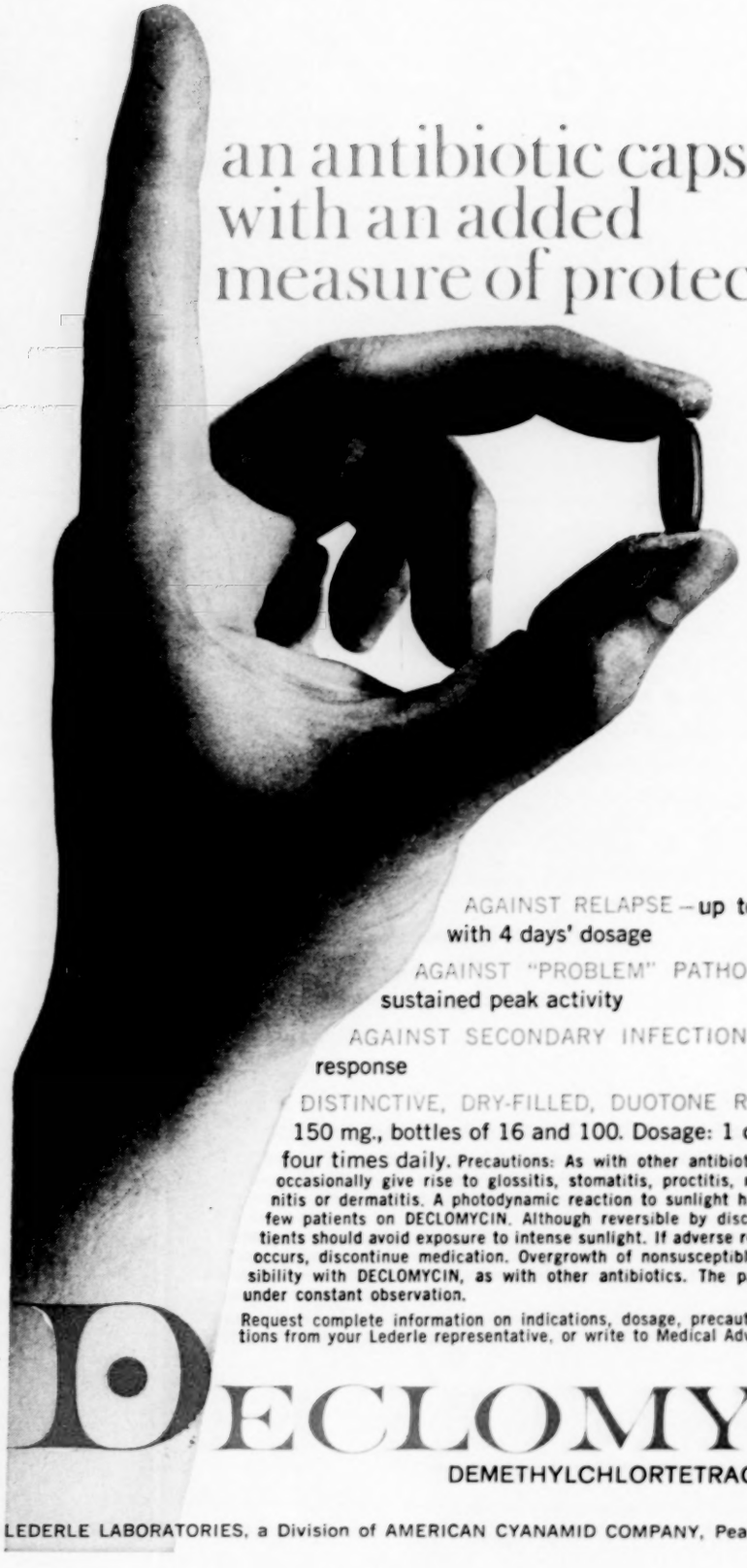
PRECAUTIONS: The use of broad-spectrum antibiotics may, in rare cases, result in an overgrowth of nonsusceptible organisms, such as monilia or staphylococci. Should such superinfection occur, therapy with Urobiotic should be discontinued and specific therapy instituted as shown by susceptibility testing. The use of sulfonamides may cause renal crystalluria or skin rash, as well as other toxic or sensitivity reactions. If any of these occur, discontinue use.

SUPPLIED: Urobiotic capsules, yellow-and-grey, bottles of 50.

Pfizer

More detailed professional information available on request.

PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York Science for the world's well-being®



an antibiotic capsule with an added measure of protection

AGAINST RELAPSE – **up to 6 days' activity with 4 days' dosage**

AGAINST "PROBLEM" PATHOGENS – **uniformly sustained peak activity**

AGAINST SECONDARY INFECTION – **full antibiotic response**

DISTINCTIVE, DRY-FILLED, DUOTONE RED CAPSULES – **150 mg., bottles of 16 and 100. Dosage: 1 capsule (150 mg.) four times daily.** Precautions: As with other antibiotics, DECLOMYCIN may occasionally give rise to glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis or dermatitis. A photodynamic reaction to sunlight has been observed in a few patients on DECLOMYCIN. Although reversible by discontinuing therapy, patients should avoid exposure to intense sunlight. If adverse reaction or idiosyncrasy occurs, discontinue medication. Overgrowth of nonsusceptible organisms is a possibility with DECLOMYCIN, as with other antibiotics. The patient should be kept under constant observation.

Request complete information on indications, dosage, precautions and contraindications from your Lederle representative, or write to Medical Advisory Department.

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no longer
detoured
by
diarrhea

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Donnatal® with Kaolin and Pectin compound

Robins

DONNAGEL's comprehensive antidiarrheal formulation gives the green light to normal activity, through its fast and dependable control of intestinal hypermotility.

Each 30 cc. (1 fl. oz.) of DONNAGEL contains:

Kaolin	6.0 Gm.	Natural belladonna alkaloids:	
Pectin	142.8 mg.	hyoscyamine sulfate	0.1037 mg.
Phenobarbital (¼ gr.)	16.2 mg.	atropine sulfate	0.0194 mg.
		hyoscine hydrobromide	0.0065 mg.

also available

DONNAGEL WITH NEOMYCIN • DONNAGEL-PG

inside as well as outside the hospital...
staphylococci usually remain sensitive to

CHLOROMYCETIN®

(chloramphenicol, Parke-Davis)

That the sensitivity patterns of "street" staphylococci differ widely from those of "hospital" staphylococci is a well-established clinical fact.[1-5] Although strains of staphylococci encountered in general practice have remained relatively sensitive to a number of antibiotics,[6] the problem of antibiotic-resistant staphylococci appears to be a threat to all patients in hospitals today. It is encouraging to note, however, "...that a relatively small percentage of strains develop resistance to chloramphenicol, despite the consumption of large amounts of this antibiotic."[7]

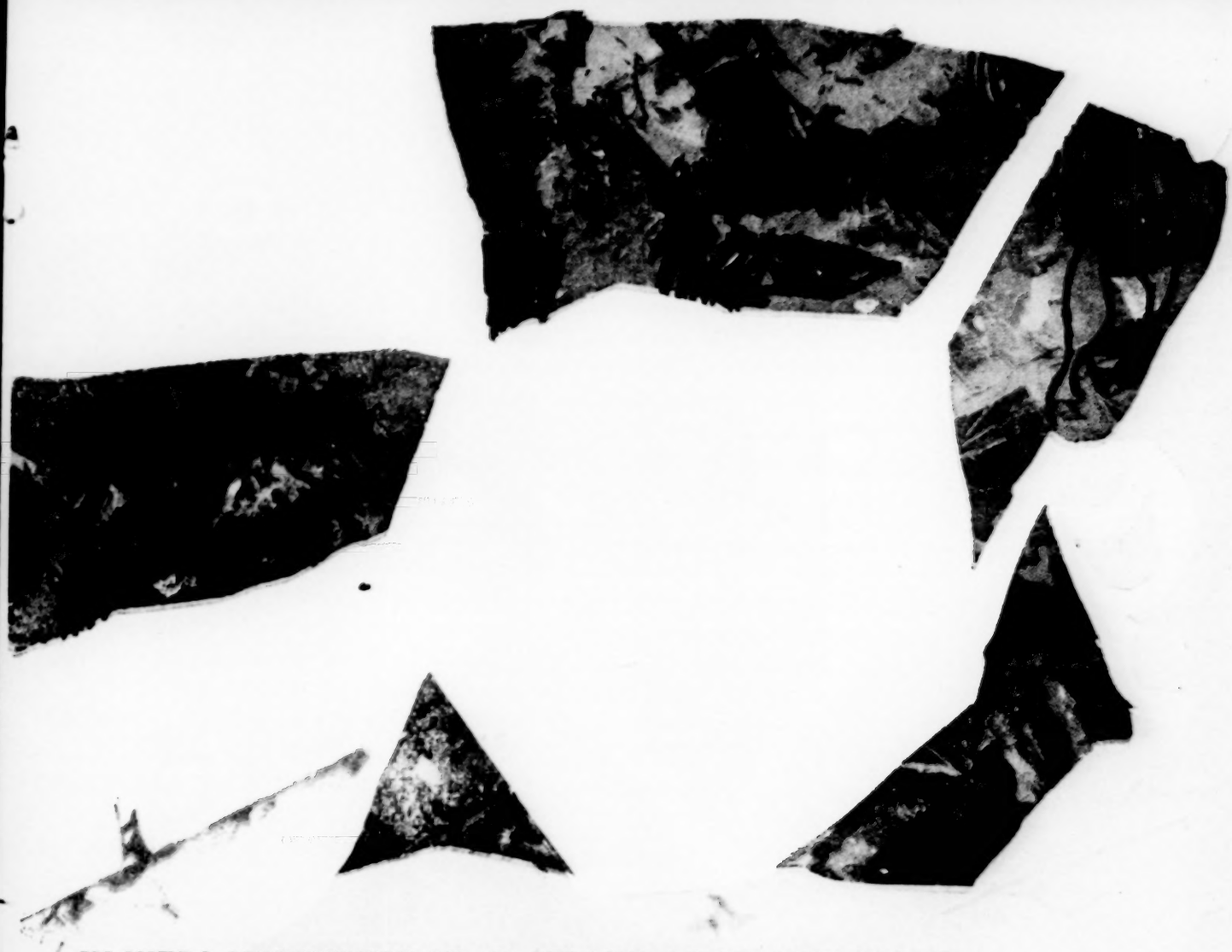
In one hospital, for example, CHLOROMYCETIN "...was the only widely used antibiotic to which few of the strains were resistant."[8] In another hospital, despite steadily increasing use of CHLOROMYCETIN since 1956, "...the percentage of chloramphenicol-resistant strains has actually been lower in subsequent years."[1] Elsewhere, insofar as hospital staphylococci are concerned, it appears that "...the problem of antibiotic resistance can be regarded as minimal for chloramphenicol."[2]

CHLOROMYCETIN (chloramphenicol, Parke-Davis) is available in various forms, including Kapseals® of 250 mg., in bottles of 16 and 100.

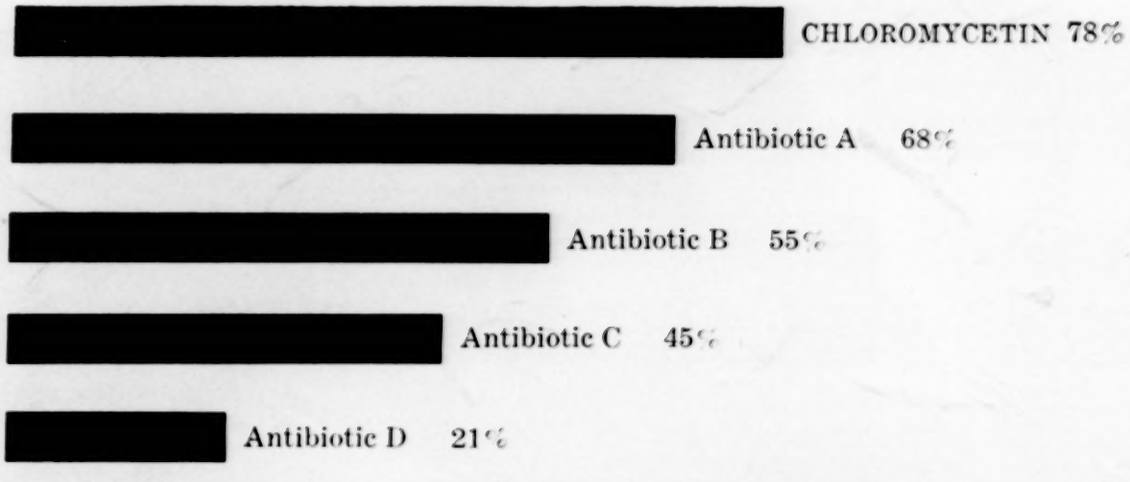
See package insert for details of administration and dosage.

Warning: Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after short-term and with prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective, or in the treatment of trivial infections such as colds, influenza, viral infections of the throat, or as a prophylactic agent.

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied upon to detect bone marrow depression prior to development of aplastic anemia.



IN VITRO SENSITIVITY OF 250 STRAINS OF STAPHYLOCOCCI TO CHLOROMYCETIN AND TO FOUR OTHER ANTIBIOTICS*



These strains of coagulase-positive staphylococci were isolated from hospitalized patients at a large county hospital during the year 1959. Sensitivity tests were done by the disc method.

*Adapted from Bauer, Perry, & Kirby[1]

References: (1) Bauer, A. W.; Perry, D. M., & Kirby, W. M. M.: *J.A.M.A.* **173**:475, 1960. (2) Fisher, M. W.: *Arch. Int. Med.* **105**:413, 1960. (3) Cohen, S.: *Circulation* **20**:96, 1959. (4) Edwards, T. S.: *Am. J. Ophth.* **48**, Part II:19, 1959. (5) Smith, I. M.: Staphylococcal Infections, Chicago, The Year Book Publishers, Inc., 1958, p. 148. (6) Petersdorf, R. G.; Rose, M. C.; Minchew, H. B.; Keene, W. R., & Bennett, I. L., Jr.: *Arch. Int. Med.* **105**:398, 1960. (7) Editorial: *J.A.M.A.* **173**:544, 1960. (8) Finland, M.; Jones, W. F., Jr., & Bennett, I. L., Jr.: *Arch. Int. Med.* **104**:365, 1959.

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for puzzling signs and symptoms...

a reliable diagnostic tool

When signs and symptoms refuse to fall into place, the C.R.P.A. test accurately indicates inflammatory and necrotic diseases. A simple office procedure taking less than two minutes to set up and perform, the C.R.P.A. test can be used *prior to other tests* to determine the necessity for an erythrocyte sedimentation rate or SGO-T level.

Unlike the ESR or SGO-T level, a C.R.P.A. test demonstrates no variability in normal values. It is influenced only by the C-reactive protein in the patient's blood. A positive reaction always indicates pathology;[1] no false positives have ever been reported.

The C.R.P.A. test is a consistently constant indicator of acute myocardial infarction,[1-9] acute rheumatic fever,[10-12] active widespread malignant disease,[1,6,7,12,13] and bacterial infections.[1,5,7,14]

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for routine blood chemistry

The reliability of the C.R.P.A. test makes it invaluable in differential diagnoses and routine work-ups. It may be used to deny or confirm ESR and SGO-T readings. Because it is so sensitive it can mark the progress of the disease and measure the effectiveness of therapy.[1,15]

References: 1. Editorial: J.A.M.A. 160:672 (Feb. 25) 1956. 2. Levinger, G. L.; Levy, H., and Elster, S. K.: Ann. Int. Med. 46:68, 1957. 3. Kroop, I. G., and Shackman, N. H.: Am. J. Med. 22:90, 1957. 4. Kroop, I. G., and Shackman, N. H.: Proc. Soc. Exper. Biol. & Med. 86:95, 1954. 5. Shubin, H.; Glaskin, A., and Heiken, C. A.: Tuberc. 15:62, 1955. 6. Losner, S., and Volk, B. W.: New York J. Med. 56:2665 (Sept. 1) 1956. 7. Roantree, R. J., and Rantz, L. A.: A.M.A. Arch. Int. Med. 96:674, 1955. 8. Goldner, F., and Meador, C.: South M. J. 48:1339, 1955. 9. Hedlund, P.: Acta med. scandinav. supp. 196:579, 1947. 10. Shackman, N. H.; Heffer, E. T., and Kroop, I. G.: Am. Heart J. 48:599 (Oct. 13) 1954. 11. Boland, E. W.: California Med. 82:65, 1955. 12. Knights, E. M., Jr.; Hutchins, M.; Morgan, E., and Ploompuu, J.: J.A.M.A. 162:9 (Sept. 1) 1956. 13. Shetlar, M. R.; Bullock, J. A.; Shetlar, C. L., and Payne, R. W.: Proc. Soc. Exper. Biol. & Med. 88:107, 1955. 14. Ruggieri, P. A.: J. M. Soc. New Jersey 52:500, 1955. 15. Dodd, K.: Mississippi Doctor 33:59, 1955.

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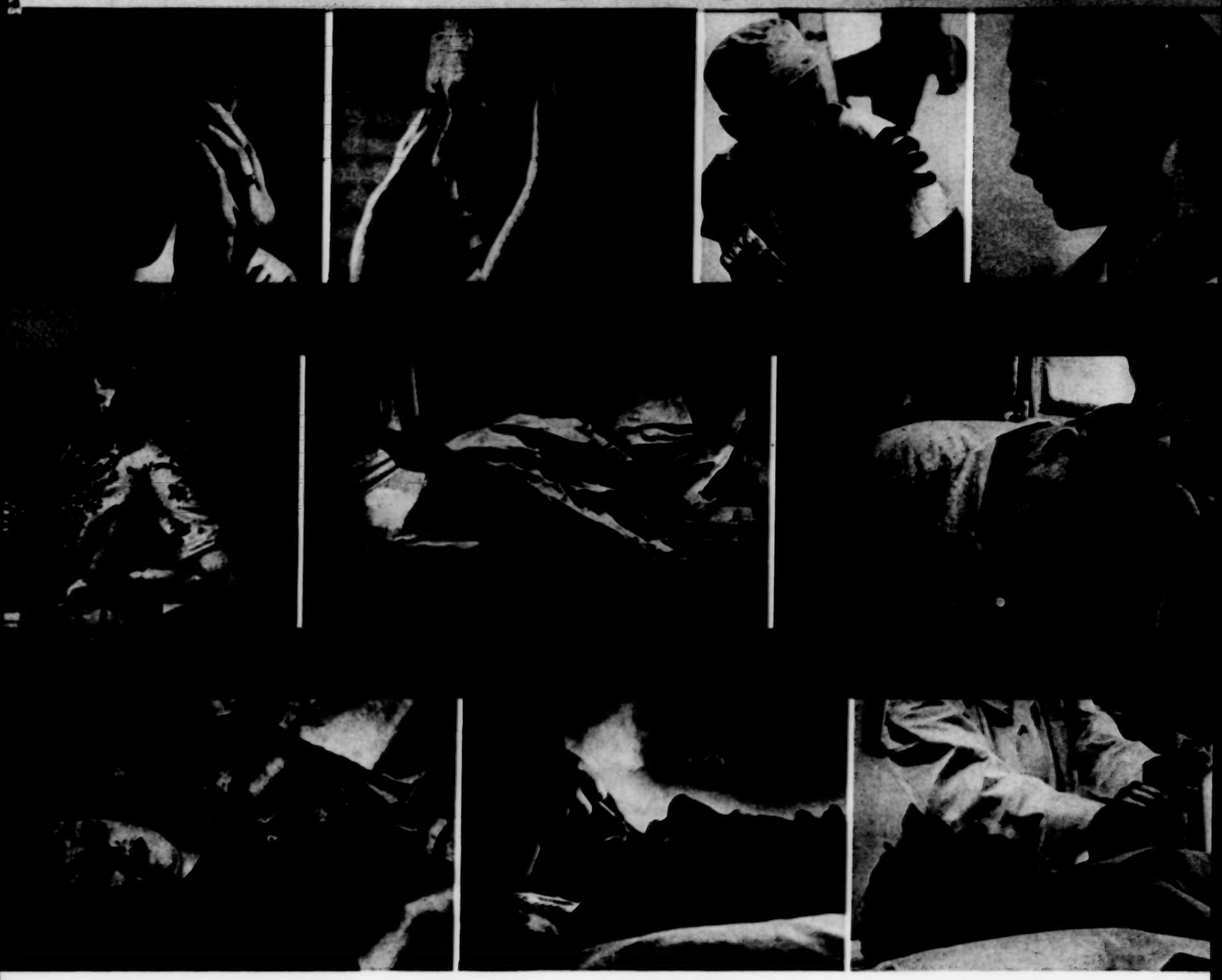
Percodan tablets effectively relieve pain through a range of



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for pain

prompt relief
profound relief
prolonged relief

ACTS FASTER—usually within 5-15 minutes. **LASTS LONGER**—usually 6 hours or more. **MORE THOROUGH RELIEF**—permits uninterrupted sleep through the night. **RARELY CONSTIPATES**—excellent for chronic or bedridden patients.

AVERAGE ADULT DOSE: 1 tablet every 6 hours. May be habit forming. Federal law permits oral prescription.

Each PERCODAN* Tablet contains 4.50 mg. dihydrohydroxycodeinone hydrochloride, 0.38 mg. dihydrohydroxycodeinone terephthalate, 0.38 mg. homatropine terephthalate, 224 mg. acetylsalicylic acid, 160 mg. acetophenetidin, and 32 mg. caffeine.

Also available—for greater flexibility in dosage—PERCODAN®-DEMI: The PERCODAN formula with one-half the amount of salts of dihydrohydroxycodeinone and homatropine.

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Endo

ENDO LABORATORIES
Richmond Hill 18, New York

*U.S. Patent Nos. 2,628,185 and 2,907,768

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Obedrin and the 60-10-70 Menu Plan provide supportive medication and a balanced eating plan *under your supervision.*

FORMULA: Tablets and Capsules

Semoxydrine HCl (Methamphetamine HCl)	5 mg.
Pentobarbital	20 mg.
Ascorbic Acid	100 mg.
Thiamine Mononitrate	0.5 mg.
Riboflavin	1 mg.
Nicotinic Acid (Niacin)	5 mg.

THE S. E. MASSENGILL COMPANY

"sure...I used a crash diet...lost five pounds and now I've gained it all back!"

but to bring weight down and keep it down...

Obedrin®

and the 60-10-70 Menu Plan

Obedrin and the 60-10-70 Menu Plan will help you successfully treat patients who *must* reduce excess pounds and *maintain* optimum weight. Obedrin aids in curbing abnormal food cravings and facilitates establishment of correct eating habits.

Dosage can be individualized so appetite will be depressed at peak hunger periods. And Obedrin is the ideal support with its

- Methamphetamine — proved anorexigenic and mood-lifting effects
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Calorie counting?

Not with the 60-10-70 Menu Plan; yet it assures balanced food intake with sufficient protein and roughage.

Write for

60-10-70 MENU PLANS, WEIGHT CHARTS AND SAMPLES OF OBEDRIN.

Supplied:

Tablets and capsules—bottles of 100, 500, and 1,000.

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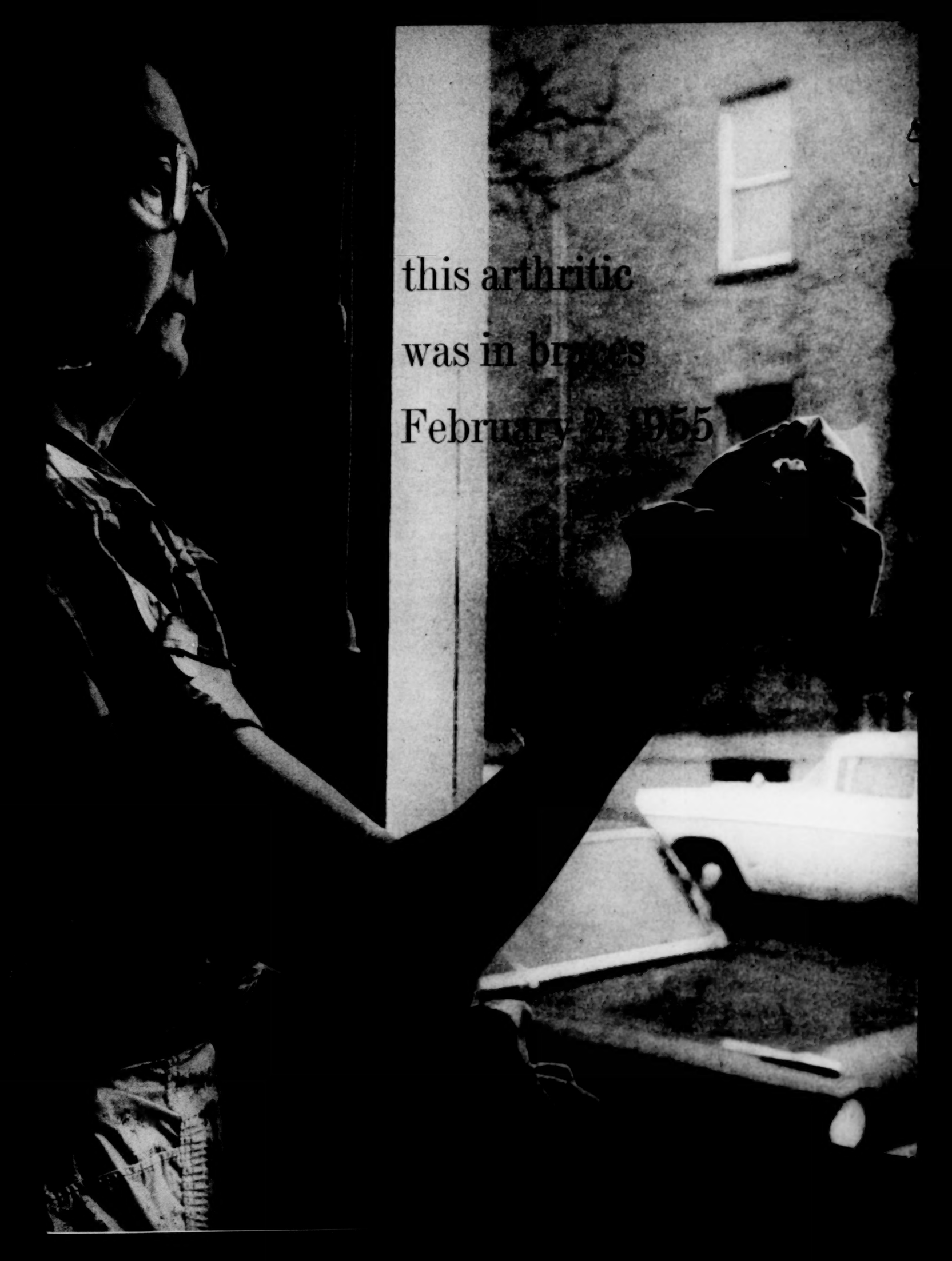
this arthritic
was in braces
February 2, 1955

Schering

maintained on Meticorten for six years she now does her own housework

H. M. first had pain in her wrists in 1940. Eventually all her peripheral joints were involved. Orthopedic surgery in 1951, 1952 and 1953 failed to restore the loss of function caused by her rheumatoid arthritis. When seen in 1954 at the age of 59, she exhibited marked deformities in her peripheral joints. Treatment with gold, phenylbutazone and cortisone had to be discontinued because of marked weight gain and moon face.

On February 2, 1955, the patient was placed on METICORTEN 5 mg. t.i.d. Eventually, she was able to discard her braces and crutches and resume a completely normal way of life. In spite of her advanced anatomical changes,

she can even use an electric mixer without discomfort.

In order to continue her improvement, she has been maintained on a dosage of 5 mg. b.i.d. In the six years since she has been on METICORTEN, the patient has had no side effects except for slight moon face and occasional purpura. As a result, she has been able to enjoy her hobbies such as crocheting and to participate in neighborhood activities.

Case history courtesy of Joel Goldman, M.D., Johnstown, Pa. These photographs of Dr. Goldman's patient were taken in her home on November 10, 1960.

METICORTEN,® brand of prednisone.

For complete details, consult latest Schering literature available from your Schering Representative or Medical Services Department, Schering Corporation, Bloomfield, N. J.

JANUARY, 1961 S-794

Gastro-intestinal disorders?

CONSIDER CITRUS PECTIN AND DERIVATIVES: *Pectin N.F., Pectin Cellulose Complex, Polygalacturonic and Galacturonic Acids*

Diarrheas, dysenteries—many other intestinal disorders—respond quickly and favorably to pharmaceutical specialties whose key ingredient is *an adequate dosage* of citrus pectin or a derivative.

Sunkist® Pectin N.F. provides a dependable therapeutic dosage of galacturonic acid—the recognized detoxicating factor. Specialty formulations of leading pharmaceutical manufacturers contain this product of Sunkist Growers.

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for a calm view of the menopause

PMB. "PREMARIN"® WITH MEPROBAMATE

provides desired tranquilization plus required estrogen replacement

PMB combines the effective calmative action of meprobamate, together with "Premarin," the most widely prescribed natural oral estrogen for specific control of menopausal symptoms.

PMB tranquilizes the overanxious and nervous patient, while "Premarin" gives prompt relief of distressing symptoms, imparts a "sense of well-being" and, in addition, exerts a protective influence in many vital processes as in cardiovascular, bone and protein metabolism.

Usual dosage: **PMB ("Premarin" with Meprobamate)—one tablet 3 times daily. Dosage is adjusted to individual requirements. Cyclic therapy is recommended (3 week regimen with 1 week rest period) to avoid continuous stimulation of breast and uterus.**

Caution: **Meprobamate may produce drowsiness in some patients, but this usually disappears with continued therapy or reduced dosage. Severe allergic reactions are rare, but if they occur, this calls for immediate withdrawal of drug and treatment (epinephrine, antihistamines, or hydrocortisone).**

Availability: No. 880—PMB-200—Each tablet contains 0.4 mg. conjugated estrogens, equine ("Premarin") and 200.0 mg. meprobamate. No. 881—PMB-400—Each tablet contains 0.4 mg. conjugated estrogens, equine ("Premarin") and 400.0 mg. meprobamate. (Both products in bottles of 60 and 500.)

***AYERST LABORATORIES** New York 16, N. Y. • Montreal, Canada*

6118

Menopausal distress: a syndrome involving all three levels of the autonomic nervous system

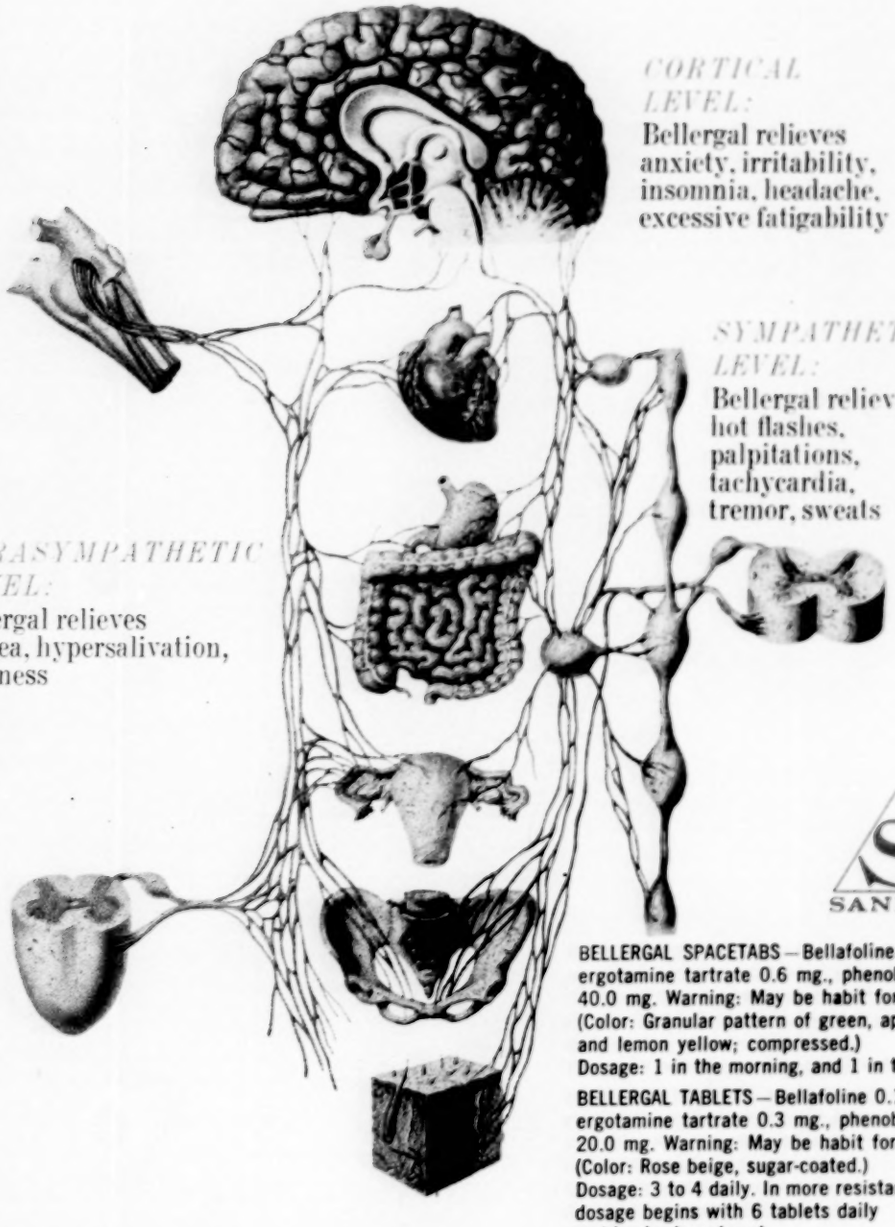
for functional disorders of the menopause

Bellergal®

SPACETABS®

stabilizes the entire autonomic nervous system

(without disturbing endocrine balance)



CORTICAL LEVEL:
Bellergal relieves anxiety, irritability, insomnia, headache, excessive fatigability

SYMPATHETIC LEVEL:
Bellergal relieves hot flashes, palpitations, tachycardia, tremor, sweats

PARASYMPATHETIC LEVEL:
Bellergal relieves nausea, hypersalivation, faintness

SANDOZ

BELLERGAL SPACETABS—Bellafoline 0.2 mg., ergotamine tartrate 0.6 mg., phenobarbital 40.0 mg. Warning: May be habit forming. (Color: Granular pattern of green, apricot and lemon yellow; compressed.)
Dosage: 1 in the morning, and 1 in the evening.

BELLERGAL TABLETS—Bellafoline 0.1 mg., ergotamine tartrate 0.3 mg., phenobarbital 20.0 mg. Warning: May be habit forming. (Color: Rose beige, sugar-coated.)
Dosage: 3 to 4 daily. In more resistant cases, dosage begins with 6 tablets daily and is slowly reduced.

INHIBITOR OF GASTRIC ACID SECRETION

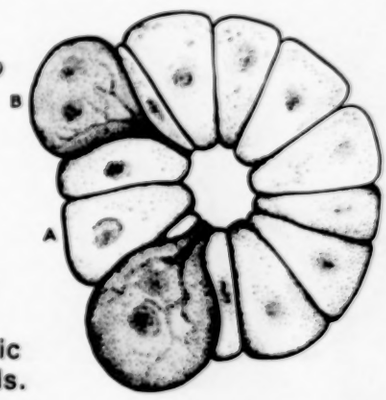
NACTON®... Has been shown to suppress gastric acid secretion for as long as 8 to 9 hours.[1] "...reduces the total output of gastric HCl by about 60%."[2]

Decreases hypermotility of stomach and bowel.[3-7]

Aids healing of peptic ulcer.[8]

Unusually low incidence of side effects.[1, 3, 9]

NACTON TABLETS...4 mg.
Average effective dose:
4 mg. three or four times daily

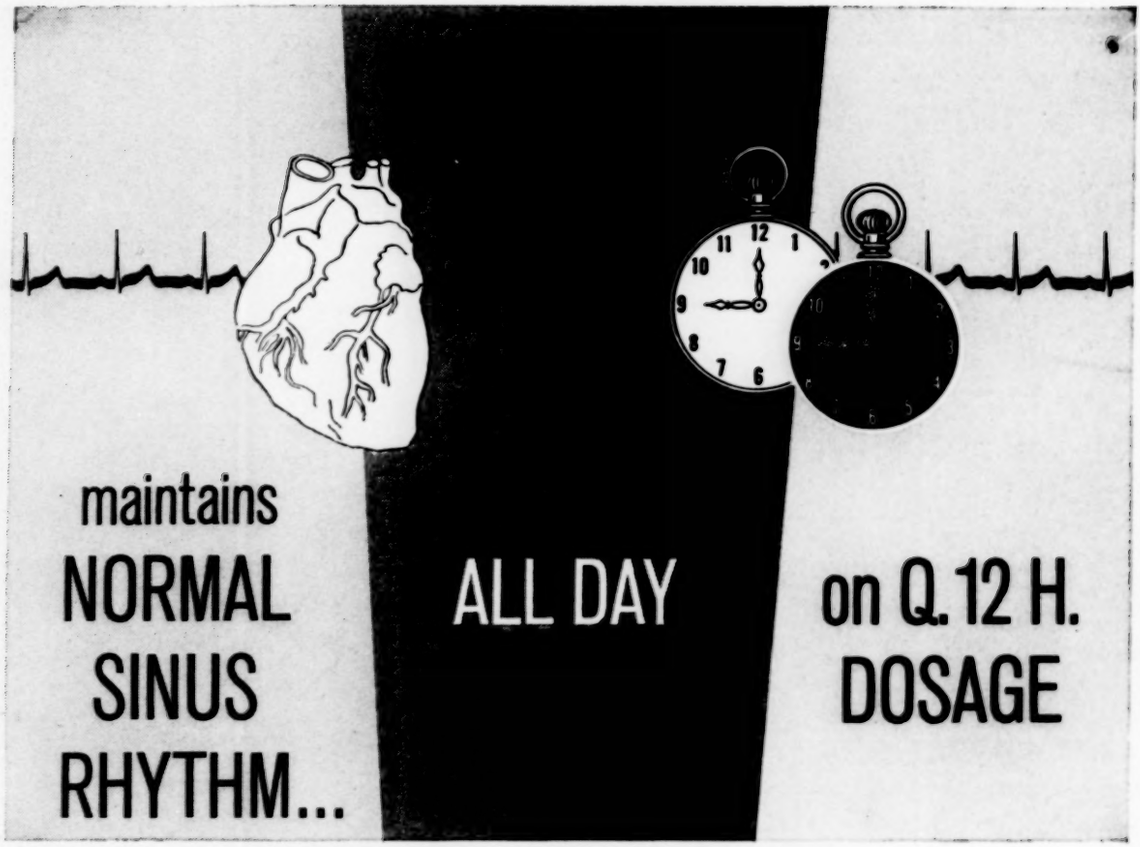


Typical gastric secretory gland.
A—chief cell (pepsin-producing).
B—parietal cell (acid-producing).
NACTON effectively inhibits gastric acid production by the parietal cells.

References:

1. Douthwaite, A. H., and Hunt, J. N.: Effect of "Nacton" in Patients with Duodenal Ulcer, Brit. Med.J. *1*:1030-1034 (May 3) 1958. 2. Douthwaite, A. H.: The Development of the Treatment of Duodenal Ulcer, Proc. Roy. Soc. Med. *51*:1063-1068 (Dec.) 1958. 3. Steigmann, F.: The Problems of Side Effects in Anticholinergic Therapy, to be published. 4. Grossman, M. I., and Tuttle, S. G.: Clinical Report to McNeil Laboratories. 5. Texter, E. C.: Clinical Report to McNeil Laboratories. 6. Cayer, D., and co-workers: Clinical Report to McNeil Laboratories. 7. Lorber, S. H.: Clinical Report to McNeil Laboratories. 8. Walker, G. F.: Therapeutics; Gastric Sedatives, Brit. J. Clin. Pract. *13*:382 (May) 1959. 9. Douthwaite, A. H., Hunt, J. N., and MacDonald, I.: A Long-Acting Inhibitor of Gastric Secretion, Brit. Med. J. *2*:275-276 (Aug. 3) 1957.

McNEIL **McNeil Laboratories, Inc. • Philadelphia 32, Pa.**



QUINAGLUTE®

DURA-TABS®

exclusive oral Sustained Medication*
Quinidine Gluconate 5 gr. (0.33 Gm.)

IN CARDIAC ARRHYTHMIAS[1-10]

Maximum efficacy: maintains effective quinidine blood levels all day, all night. **Better tolerated:** because quinidine gluconate is 10 times as soluble as the sulfate, and only part of daily Dura-Tab dosage contacts gastric mucosa. **Maximum convenience:** given q. 12 h.—no night dosage needed.

DOSAGE: for conversion of auricular fibrillation to normal sinus rhythm, **in most cases,** 2 Dura-Tabs 3 or 4 times a day, for 2 to 3 days; longer periods are required in some patients. **For maintenance,** 2 Dura-Tabs q. 12 h. in most patients . . . Bottles of 30, 100 and 250 Quinaglute Dura-Tabs.

For SAMPLES and complete literature[1-10] giving indications, cautions, etc., write

REFER TO PDR Page 821

WYNN PHARMACAL CORPORATION
Lancaster Ave. at 51st St., Philadelphia, Pa.

*U.S. Patent 2,895,881

also available **INJECTABLE QUINAGLUTE**

METRECAL AND OBESITY

A DISCUSSION: PART I

the first of two parts of a discussion on the significance
of Metrecal in the management of obesity

THE EDWARD DALTON COMPANY
A Division of Mead Johnson & Company

METRECAL AND OBESITY

From the time of its introduction in late autumn of 1959, the professional acceptance of Metrecal brand dietary for weight control—the product and the concept—has been widespread and sustained.

During this brief interval a considerable body of successful experience has accrued—both from clinical studies and physician observation.

During the same period, many questions have arisen (some fundamental) and have gained some attention, with relation to the safety and efficacy of the product in the personal and professional management of obesity.

The incidence of such questions is not unexpected in view of the fact that Metrecal is an essentially simplified approach to overweight, a problem that (1) is one of the oldest of the chronic ills of man, (2) is widespread in the United States today in the sense of including virtually half of the adult population, and (3) is dangerous both as such and for the degree to which it aggravates other disease entities.

These questions have resulted in an element of confusion which has been compounded by a host of products which (while seemingly imitative to the concept) offer a wide degree of variability in (1) their nutritional composition, (2) the extent of their technical validation, and (3) the responsibility of their accompanying claims.

This, therefore, is the first of a discussion in two parts, prepared expressly for the medical and allied professions.

Part I of this DISCUSSION begins with a restatement of certain aspects of obesity which are fundamental to sound diagnosis and therapy, notwithstanding the apparently elementary principles they represent. With these clearly in mind, Metrecal, both concept and product, will thereafter be evaluated in detail.

Part II of this DISCUSSION will be published shortly in this journal and will be concerned with clinical evidence and other supportive data which clearly substantiate the medical and nutritional rationale for Metrecal as presented here. In these terms, it should be possible objectively and constructively to comment on such topics, as: (1) its safety and effectiveness for short- and long-term use; (2) practicability in use in comparison with restricted diet or appetite-depressant drugs, and (3) whether it militates against the return to so-called "usual foods" or dietary regimens conducive to the cohesiveness of the family as a social unit.

Metrecal is supported on a continuing basis by clinical investigations of considerable scope and penetration. The practice-oriented data resulting from these studies will be similarly presented from time to time as a service to the medical and allied professions, in future issues of this journal.

OBESITY

Elementary considerations

Obesity is due to the intake of more energy than is expended, *i.e.*, simple overeating as compared to needs.

When seeing an obese patient for the first time, a physician's thoughts may be summarized as follows:

Why is the patient obese?

Is obesity due to psychological or emotional factors? neurosis? loneliness? disappointment? boredom? compulsion? or *is* it due to an attempt to escape from an unfeeling world?

Is overeating related to the eating habits of the family?

Is there an endocrine imbalance as a basis for obesity?

Is obesity in this patient a familial tendency? Are siblings likewise obese?

Is the patient a between-meal "nibbler"?

How can I most successfully persuade this patient to reduce?

I can *advise*, and *encourage*;

I can *appeal* to a desire for an improved appearance;

I can *frighten* with facts on the susceptibility of obese older persons to degenerative diseases (such as diabetes, arteriosclerosis and heart disease);

I can *emphasize* the increased comfort and mobility that comes from reducing—no more abdominal supports, or tight-fitting clothes, or wheezing, or being laughed at;

Since obesity is a symptom, I can try to *determine* the primary cause and establish a reasonable goal (weight loss, and at least partial resolution of the primary cause) toward which the patient can strive;

I can *emphasize* the decreased life expectancy of the obese;

I can *explain* the increased risk, and longer convalescence, if extensive surgery is ever needed.

What are the real dangers (or "costs") of overweight?

1. Increased rate of mortality (shorter life on the average);
2. Appearance not as socially acceptable;
3. Reduced physical capacity and mobility;
4. Increased susceptibility to certain degenerative diseases: diabetes, arteriosclerosis, heart disease;
5. Increased surgical risk.

What can I do to aid this patient?

Prescribe drugs to reduce appetite! But I know their effects are short-lived and they may have some undesirable reactions.

Undertake psychotherapy! But this is time-consuming and expensive. I can be most effective by just listening and counseling.

Suggest a low-calorie diet of usual foods! But this usually is not very successful because what is intended as a 1000-calorie diet may end up as a 2000-calorie intake, and the patient gets discouraged because significant weight loss is not achieved. I haven't time to discuss with each patient the thermal qualities of each food and its calorie equivalent—and most patients couldn't care less.

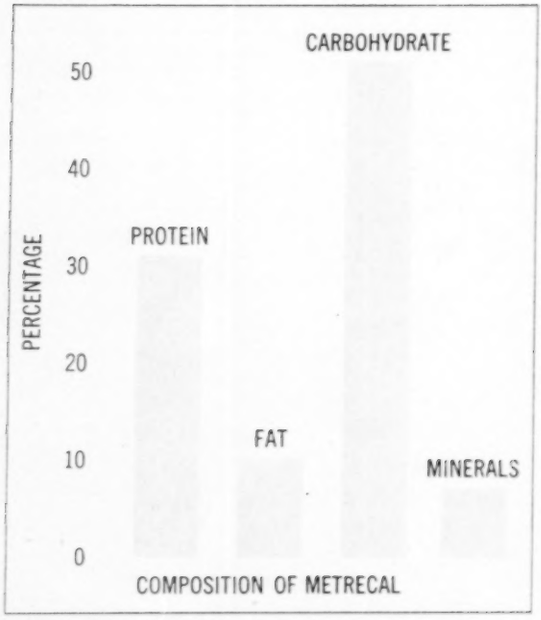
Educate the patient to proper eating habits! This is the essence of the problem. To develop adequate motivation, significant weight loss must be attained *promptly*, without excessive *hunger*, with adequate *nutrition*, with a minimum of *temptation*, and with the avoidance of *decisions* on whether to eat or not to eat attractive high-calorie foods, and how much.

Now, the physician can prescribe a dietary for weight control that was designed to meet the basic medical objectives necessary for intelligent management of the obese patient. This means the complete substitution of a measured amount of a nutritionally adequate food for all usual foods for a period of time.

WHAT IS METRECAL?

The abbreviated charts on the following pages describe the composition, analysis, essential features, and qualities of Metrecal dietary for weight control. These seemingly elementary considerations describe a product designed to meet a widespread therapeutic need; adequately, uniquely, safely, and simply.

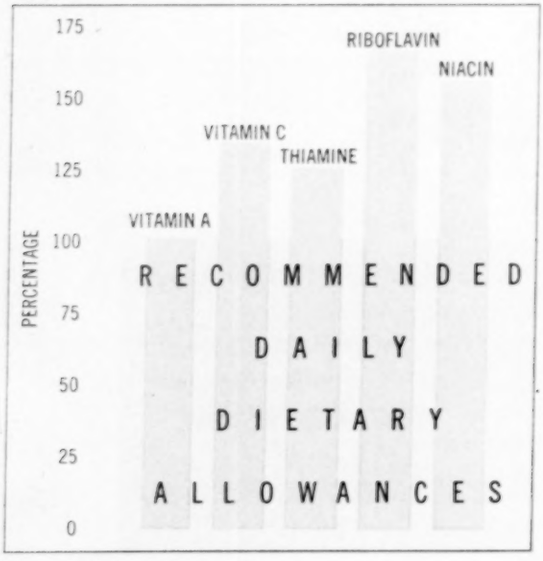
CHART I



the composition of Metrecal

Metrecal contains a high percentage of protein and a moderate amount of fat. These contribute to the **appetite- and hunger-satisfying** qualities of Metrecal.

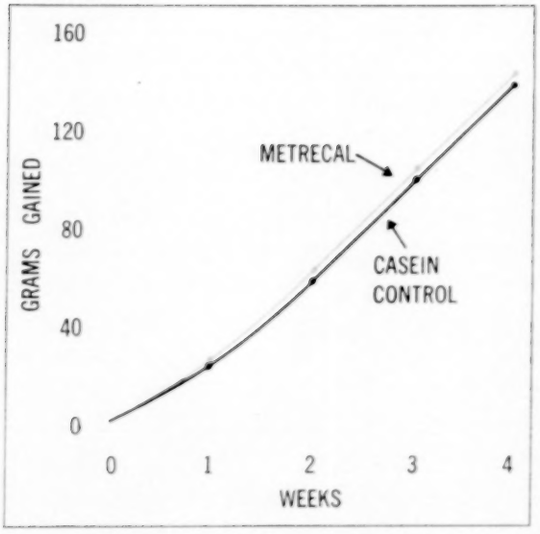
CHART II



vitamins in Metrecal

Metrecal supplies even more vitamins than recommended for the average adult. **Vitamins** are essential to health, and all are present in adequate amounts in Metrecal.

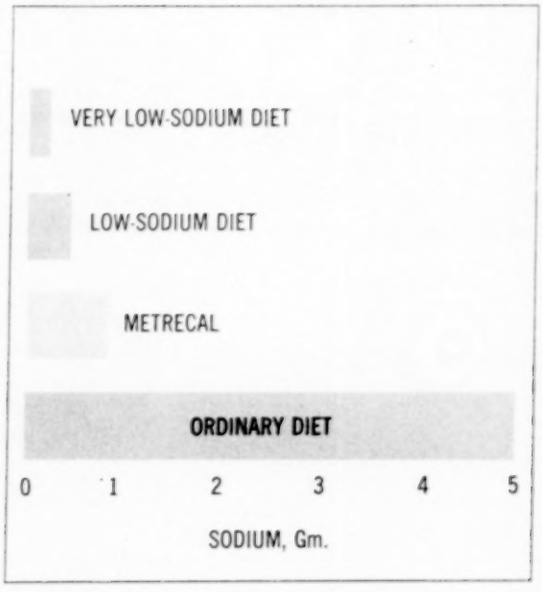
CHART III



Metrecal is nutritionally complete

The rate and amount of gain in body weight are identical for growing rats fed Metrecal or a casein control ration **ad libitum**. This indicates that Metrecal is a **nutritionally complete** food.

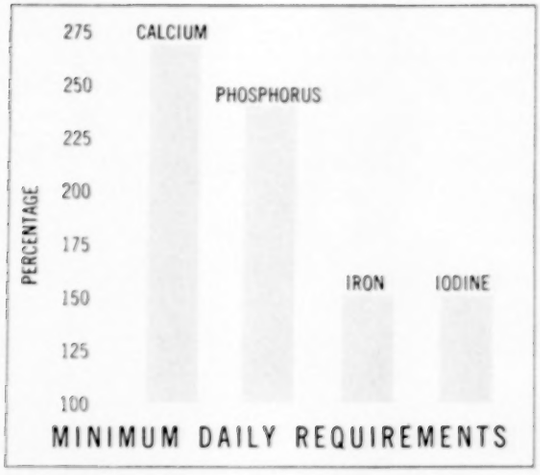
CHART IV



sodium content of Metrecal

Metrecal supplies approximately 900 mg. of **sodium** per 900 calories. This is a desirable intake for obese or hypertensive patients. Where profuse sweating occurs, the ingestion of additional salt may be specified.

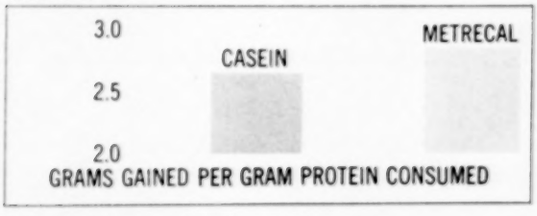
CHART V



minerals in Metrecal

Metrecal provides from 150% to 266% of the Minimum Daily Requirements for **calcium, phosphorus, iron and iodine.** Metrecal also supplies adequate amounts of all other minerals known to be required by normal persons.

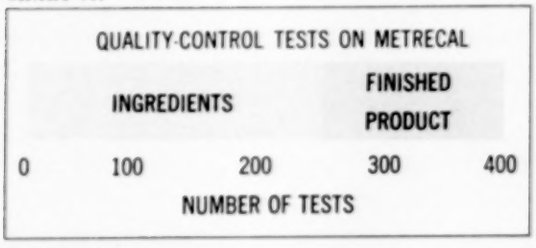
CHART VI



Metrecal protein is nutritious

Evaluation of the nutritional quality of the protein in Metrecal shows that the **protein is as nutritious as casein**—the standard for such studies.

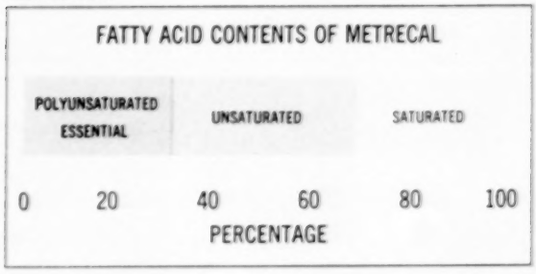
CHART VII



Metrecal is a quality product

Metrecal is **tested thoroughly**—396 tests and assays are completed before Metrecal is released.

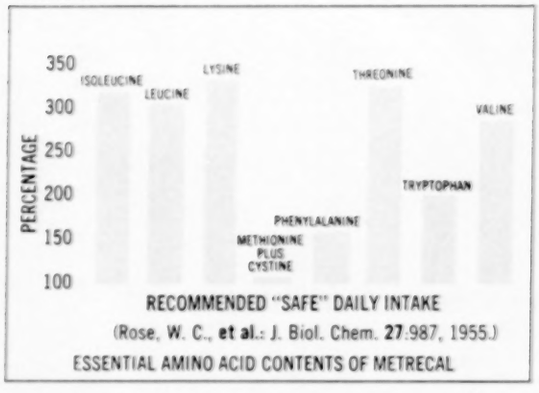
CHART VIII



essential fatty acids in Metrecal

Metrecal supplies ample quantities of the **polyunsaturated** "essential **fatty acids.**" Linoleic and linolenic acids constitute 33% of the fatty acid contents of Metrecal, and more than ⅔ of the fatty acids in Metrecal are unsaturated.

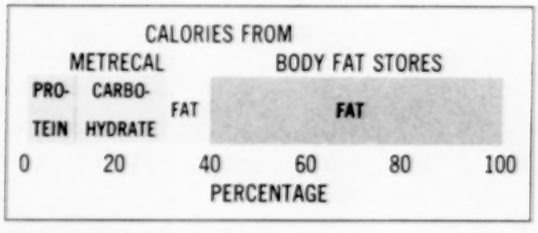
CHART IX



amino acid content of Metrecal is ample

Metrecal supplies significant amounts of all amino acids, including **ample quantities of each amino acid** which is essential in human nutrition.

CHART X



Metrecal is effective

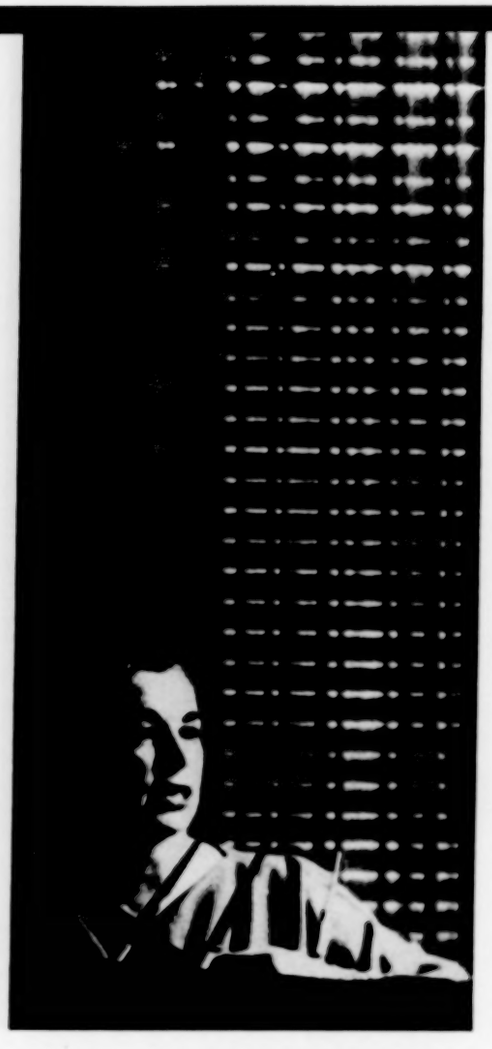
Calories are required to maintain body temperature and support muscular activity. If an obese sedentary person requires 2300 calories and ingests 900 calories as Metrecal, there will be a "calorie deficit" of 1400 calories. This will be met by oxidation of body fat, as shown in the chart. Such a person, limited strictly to 900 calories per day as Metrecal, would **lose 2.4 pounds of fat each week.**

METRECAL AND OBESITY

The foregoing Part I of a DISCUSSION on the above subject has summarized certain elementary concepts on obesity and defined Metrecal.

In Part II of this DISCUSSION, to be published soon in this journal, the Edward Dalton Company will summarize the clinical data[1-4] validating the effectiveness of Metrecal, and comment on certain misconceptions arising from its successful attack on the problem of obesity in American life.

References: (1) Antos, R. J.: Southwestern Med. *40*:695-697 (Nov.) 1959. (2) Roberts, H. J.: Am. J. Clin. Nutrition *8*:817-832 (Nov.-Dec.) 1960. (3) Tullis, I. F.: J. Mississippi M. A. *1*:636-638 (Dec.) 1960. (4) Tullis, I. F. and Allen, C. E.: Clinical Experiences with a Simple Weight-Reducing Formula, Current Therapeutic Research, in press.



symptoms gone... feels like a new woman

basic therapy in vaginitis eliminates symptoms · itching · burning · leukorrhea · malodor · destroys pathogens · Trichomonas vaginalis · Candida (Monilia) albicans · nonspecific organisms...alone or in combination · has these advantages · high rates of clinical and cultural cures · effectiveness even in menstrual blood and vaginal debris · safe and nonirritating to delicate inflamed tissue · esthetically acceptable with no disagreeable staining

TRICOFURON®

(nifuroxime and furazolidone) **Improved**

Powder / Suppositories

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Division of The Norwich Pharmacal Company
NORWICH, NEW YORK

Many **MIGRAINE** attacks can be **stopped at the start** by the prompt use of...

'MIGRAL'®

Advantage

'MIGRAL' permits maximum ergotamine therapy with the first dose —because the 'MIGRAL' formula includes the proved antiemetic, cyclizine hydrochloride, to counteract the tendency to nausea and vomiting.

Dosage

'MIGRAL' should be taken immediately at the start of a migraine attack, and the effective dosage should be determined on an individual basis. When the total dosage necessary to stop an attack has been determined, that amount should be taken as initial dosage in subsequent attacks.

In general, 2 to 4 'MIGRAL' tablets taken at the first sign of an attack will terminate a headache by preventing progression to the vasodilation stage. If treatment is not started sufficiently early to achieve this result, an additional 1 or 2 tablets should be administered every half hour until the patient is relieved, or until a total dosage of 6 tablets has been taken.

Caution

It is recommended that not more than 6 tablets be taken during a single attack, nor more than 10 tablets per week.

Each sugar-coated 'MIGRAL' tablet provides:

Ergotamine Tartrate	1 mg.
'Marezine'® brand Cyclizine Hydrochloride	25 mg.
Caffeine	50 mg.

In bottles of 20 and 100 tablets.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

Why combining Serpasil® with Esidrix® improves control of high blood pressure

Serpasil alone often relieves vasoconstriction and decreases arterial pressure in hypertensive patients. In many cases, however, excess fluid and sodium in the arteriolar environment can keep constricted blood vessels from dilating fully in response to antihypertensive therapy. By depleting excess fluid and sodium, Esidrix makes the vasculature more sensitive to other antihypertensive agents, thus enabling blood vessels to dilate to near-normal limits. When Serpasil is combined with

Hypertension plus congestive failure controlled with Serpasil-Esidrix

Mr. H. V., a 61-year-old retired pharmacist, suffers from hypertensive arteriosclerotic heart disease. In 1957 he was hospitalized after a myocardial infarction.

In addition to high blood pressure (range: 176/100 to 184/106 mm. Hg) the patient had associated congestive failure—with ankle edema and dyspnea.

Esidrix, peripheral resistance is reduced and blood pressure goes down – often to lower levels than can be achieved with single-drug therapy.

SUPPLIED: *Tablets* #2 (light orange), each containing 0.1 mg. Serpasil and 50 mg. of Esidrix; bottles of 100. *Tablets* #1 (light orange), each containing 0.1 mg. Serpasil and 25 mg. Esidrix; bottles of 100.

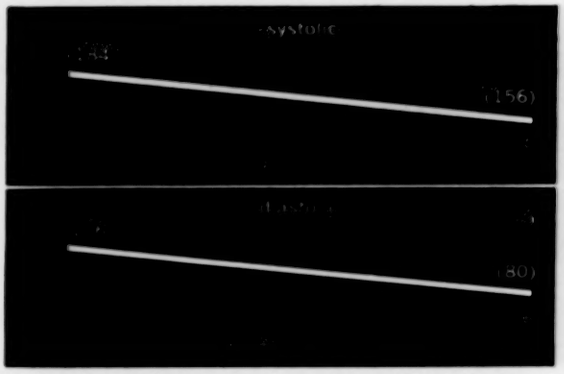
Complete information sent on request. [redacted] SUMMIT-NEW JERSEY

Serpasil®-Esidrix®

(reserpine and hydrochlorothiazide CIBA)

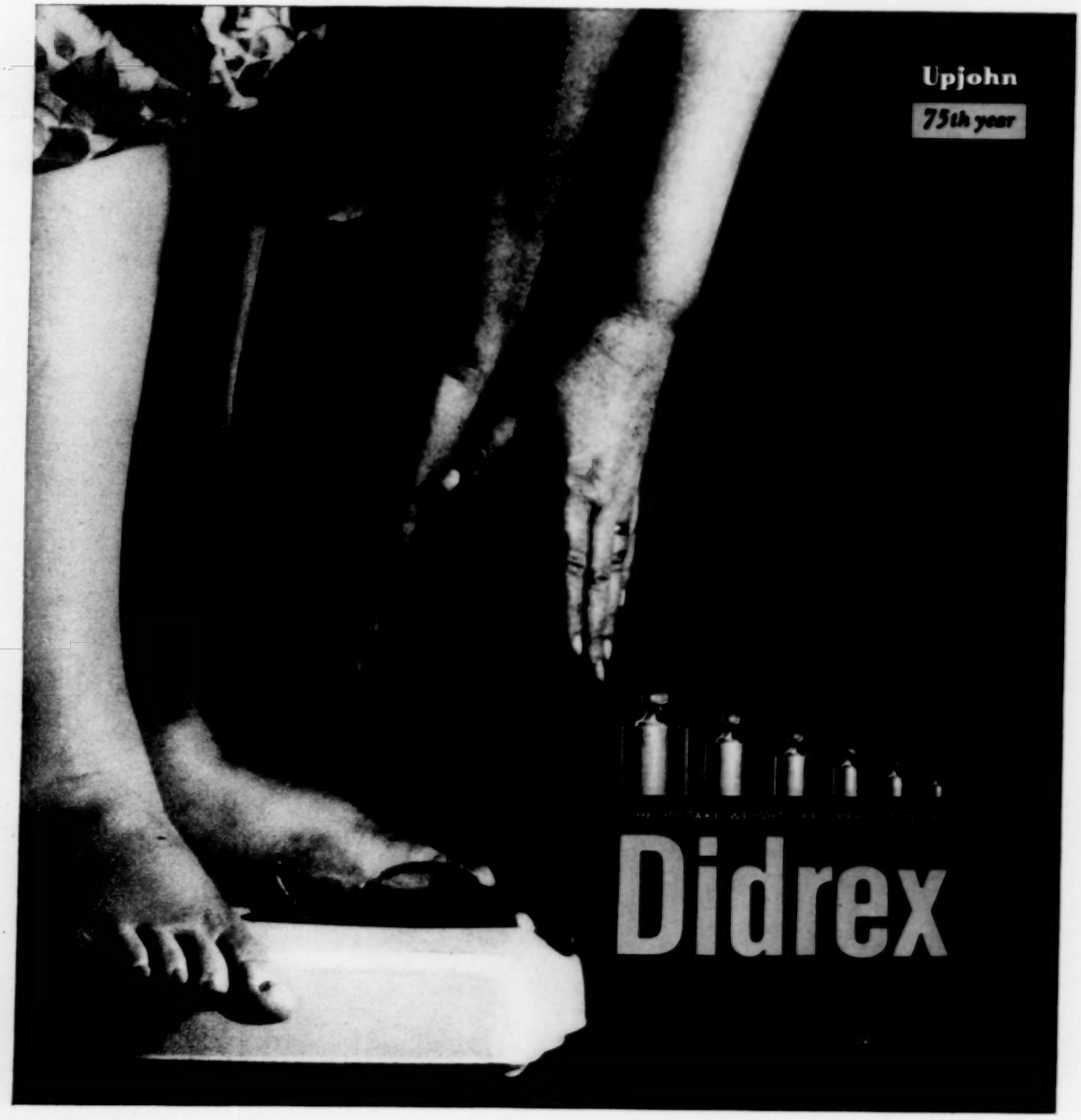
Potentiated antihypertensive effect, single-tablet convenience

On April 4, 1959, Serpasil-Esidrix Combination Tablets #1 were added to the patient's existing regimen of digitalis and a low-salt diet. On Serpasil-Esidrix, blood pressure was lowered to a range of 156/80 to 166/84 mm. Hg. Examination on May 18, 1959, revealed no evidence of congestive failure. Neck veins were no longer distended, nor was there any ankle edema.



In the first six weeks of treatment with Serpasil-Esidrix, systolic and diastolic pressures decreased steadily. Blood pressure is now stabilized at a satisfactory level.

Mr. V. has had no side effects from Serpasil-Esidrix. His tolerance for exercise has increased; he can climb stairs without shortness of breath. Mr. V. gets around more easily and generally feels better.



Didrex doesn't perform miracles... it just helps the obese patient do it herself.

The reason is simple: persistent, significant loss of weight, up to 30 weeks in reported cases, helps to preclude the "weight plateau" that so often discourages dieters after a few weeks. Thus, time and will become your allies in changing the patient's dietary habits built over months or years of weight accumulation. Didrex may be used in closely supervised diabetic, coronary insufficient, and hypertensive patients.

BRIEF BASIC INFORMATION

Description: Didrex is the Upjohn brand of benzphetamine hydrochloride [(+)-N-benzyl-N, α-dimethyl-phenethylamine hydrochloride]. A sympathomimetic compound with marked anorectic action and relatively little stimulating effect on the CNS or cardiovascular system.

Indications: Control of exogenous obesity.

Contraindications: None known to date. However, use with caution in moderate or severe hypertension, thyrotoxicosis, acute coronary disease, or cardiac decompensation.

Dosage: Initiate appetite control with ½ to 1 tablet (25 to 50 mg.) in mid-morning or mid-afternoon, according to the patient's eating habits for several days. Then "adjust" dosage to suit each patient's needs to a maximum of 3 tablets daily (150 mg.).

Side Effects: No effects on blood, urine, renal or hepatic functions have been noted. Minimal side effects have been observed occasionally: dry mouth, insomnia, nausea, palpitations and nervousness.

Supplied: 50 mg., benzphetamine hydrochloride, press-coated, scored tablets, in bottles of 100 and 500.

*Trademark—brand of benzphetamine hydrochloride, Upjohn.

References: 1. Stough, A. R.: Weight loss without diet worry: use of benzphetamine hydrochloride (Didrex). Journal of the Oklahoma State Medical Association, 53:760-767 (November) 1960. 2. Oster, H., and Medlar, R.: A clinical pharmacologic study of benzphetamine (Didrex), a new appetite suppressant. Arizona Medicine, 17:398-404 (July) 1960. 3. Simkin, B., and Wallace, L.: A controlled clinical trial of benzphetamine (Didrex). Current Therapeutic Research, 2:33-38 (February) 1960.

LOWERING

for diabetic patients

Since linoleic acid is the principal polyunsaturated fatty acid in the vegetable oils which lower blood cholesterol, there seems to be no doubt that linoleic acid is the key factor in reducing serum cholesterol through diet. The facts are clearly stated in a recent JAMA editorial:

"It is accepted generally that specific alteration in the diet will lower the concentration of cholesterol in the blood. The most effective results to date have been achieved by increasing consumption of polyunsaturated fatty acids, particularly linoleic acid ...they must replace rather than supplement some of the saturated fats and oils already in the diet."[2]

Very recent research indicates that use of Emdee Margarine in place of other spreads and shortenings may significantly contribute to reduction of serum cholesterol in diabetic patients,[1] as it has been observed to do in other patient groups.[3,4]

Emdee Margarine contains significantly more linoleic acid than any other margarine—including those promoted as "pure corn oil margarines." And, published scientific reports[3,4,5] attest to the value of Emdee Margarine in cholesterol-lowering diets. To date, no comparable studies with other margarines have been published.

REFERENCES:
1. Alterman, S. L.: Postgrad. Med. 28:112 (Aug.) 1960.
2. Pollack, H.: J.A.M.A. 172:1164 (Mar. 12) 1960.
3. Terman, L. A.: Geriatrics 14:111 (Feb.) 1959.
4. Boyer, P. A., Jr.; Lowe, J. T.; Gardier, R. W., and Ralston, J. D.: J.A.M.A. 170:257 (May 16) 1959.
5. Jolliffe, N.; Ringler, S. H., and Archer, M.: Am. J. Clin. Nutrition 7:451, 1959.

The linoleic acid-sparing process for manufacturing Emdee Margarine is unique (U.S. Patent No. 2,890,959). To protect flavor and texture, Emdee Margarine is packaged in cans and kept under refrigeration.

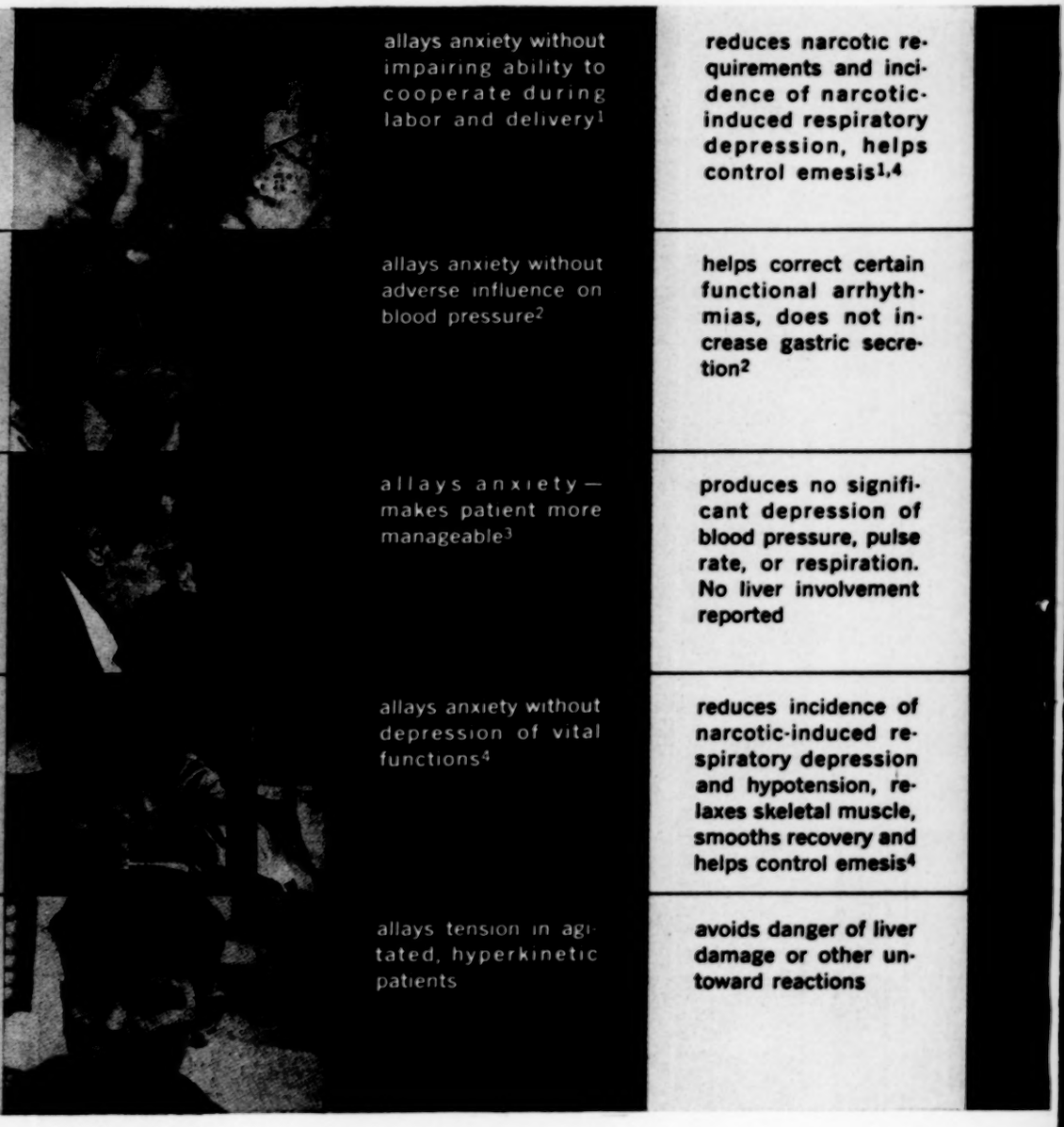
EMDEE®

margarine
in place of other
shortenings
and spreads

PITMAN-MOORE COMPANY DIVISION OF ALLIED LABORATORIES, INC., INDIANAPOLIS 6, INDIANA

Notable Success with VISTARIL...

in prepartum tension and anxiety	allays anxiety without impairing ability to cooperate during labor and delivery[1]	**reduces narcotic requirements and incidence of narcotic-induced respiratory depression, helps control emesis[1,4]**
in the cardiac or the hypertensive patient	allays anxiety without adverse influence on blood pressure[2]	**helps correct certain functional arrhythmias, does not increase gastric secretion[2]**
in problem drinkers	allays anxiety—makes patient more manageable[3]	**produces no significant depression of blood pressure, pulse rate, or respiration. No liver involvement reported**
in preoperative tension and anxiety	allays anxiety without depression of vital functions[4]	**reduces incidence of narcotic-induced respiratory depression and hypotension, relaxes skeletal muscle, smooths recovery and helps control emesis[4]**
in pediatrics	allays tension in agitated, hyperkinetic patients	**avoids danger of liver damage or other untoward reactions**



References: 1. Benson, C., and Benson, R. C.: Scientific Exhibit, Illinois Acad. Gen. Practice, Sept., 1960. **2.** Salmons, J. A.: Dis. Chest 38:105, 1960. **3.** Major, R. A.: GP 21:104, 1960. **4.** Grady, R. W., and Rich, A. L.: Scientific Exhibit, Am. Soc. Anesth., New York, Oct. 4-7, 1960.

for successful
tranquilization—

Vistaril

ORAL/HYDROXYZINE PAMOATE
PARENTERAL HYDROXYZINE [illegible]

effectively allays anxiety

no reported incidence of liver damage, respiratory depression or addiction

exerts helpful antiemetic, antisecretory, antipruritic effects

Science for the world's well-being®

Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, New York

IN BRIEF

Vistaril is hydroxyzine pamoate. The hydrochloride salt of hydroxyzine is used in the parenteral solution.

Vistaril acts rapidly in the symptomatic treatment of a variety of neuroses and other emotional disturbances manifested by anxiety, apprehension or fear—whether occurring alone or complicating a physical illness. Used preoperatively and prepartum, Vistaril controls anxiety and fear, permits a substantial reduction in the amount of meperidine or other narcotic required for satisfactory analgesia, and helps prevent emesis. Vistaril's calming effect usually does not impair discrimination, and is accompanied by direct and secondary muscle relaxation. No toxicity has been reported with Vistaril, and it has a remarkable record of freedom from reactions.

INDICATIONS: Vistaril is clinically effective in anxiety and tension states, senility, anxiety associated with various disease states, alcoholism, pre- and postpartum and pre- and postoperative tension and emesis, certain functional arrhythmias, and pediatric behavior problems.

ADMINISTRATION AND DOSAGE: Dosage varies with the state and response of each patient, rather than with weight and should be individualized by the physician for optimum results. *Recommended oral dosage:* In anxiety and tension states, senility, alcoholism, pre- and postoperative and pre- and postpartum tension and emesis: up to 400 mg. daily in divided doses. In anxiety associated with asthma, neurodermatoses, menopausal syndrome, digestive disorders, functional or essential hypertension, tension headaches: 50 mg. q.i.d. initially—adjust according to response. In cardiac arrhythmias: initial—25 mg. q. 6 h. until arrhythmia disappears; maintenance or prophylactic—50-75 mg. daily in divided doses. In pediatric behavior problems under 6 years: 50 mg. daily in divided doses. Six and over: 50-100 mg. daily in divided doses. *Recommended parenteral dosage:* In preoperative, obstetrical, and more emergent situations in other indications: 25-100 mg. I.M. or I.V. q. 4 h., p.r.n. In cardiac arrhythmias: 50-100 mg. I.M. stat, and q. 4-6 h., p.r.n.; maintain with 25 mg. b.i.d. or t.i.d.

SIDE EFFECTS: Drowsiness may occur in some patients; if so, it is usually transitory, disappearing within a few days of continued therapy or upon reduction of dosage. Dryness of mouth may be encountered at higher doses.

PRECAUTIONS: The potentiating action of hydroxyzine should be taken into account when the drug is used in conjunction with central nervous system depressants. Do not exceed 1 cc. per minute I.V. Do not give over 100 mg. per dose I.V. Parenteral therapy is usually for 24-48 hours, except when, in the judgement of the physician, longer-term therapy by this route is desirable.

SUPPLIED: VISTARIL *Capsules* (hydroxyzine pamoate)—25, 50, and 100 mg. VISTARIL *Oral Suspension* (hydroxyzine pamoate)—25 mg. per 5 cc. teaspoonful. VISTARIL *Parenteral Solution* (hydroxyzine hydrochloride)—10 cc. vials, 25 mg. per cc.; 2 cc. ampules, 50 mg. per cc.

More detailed professional information available on request.

Vertigo is reversible

Antivert® STOPS VERTIGO

moderate to complete relief of symptoms in 9 out of 10 patients'

Prescribe one ANTIVERT tablet (or 1-2 teaspoonfuls ANTIVERT syrup) 3 times daily, before each meal, for prompt relief of vertigo, Meniere's syndrome and allied disorders. Side effects are short-lived, usually only harmless flushing and tingling associated with vasodilation. ANTIVERT is contraindicated in severe hypotension and hemorrhage.

Supplied: Small blue-and-white scored tablets (meclizine HCl 12.5 mg. and nicotinic acid 50 mg.) in bottles of 100. Syrup in pint bottles. Prescription only. Bibliography available on request.

And for your aging patients—
NEOBON® Capsules: five-factor geriatric supplement.

Reference: 1. Scal, J. C.: Eye Ear Nose & Throat Month. **38**:738 (Sept.) 1959.

ROERIG

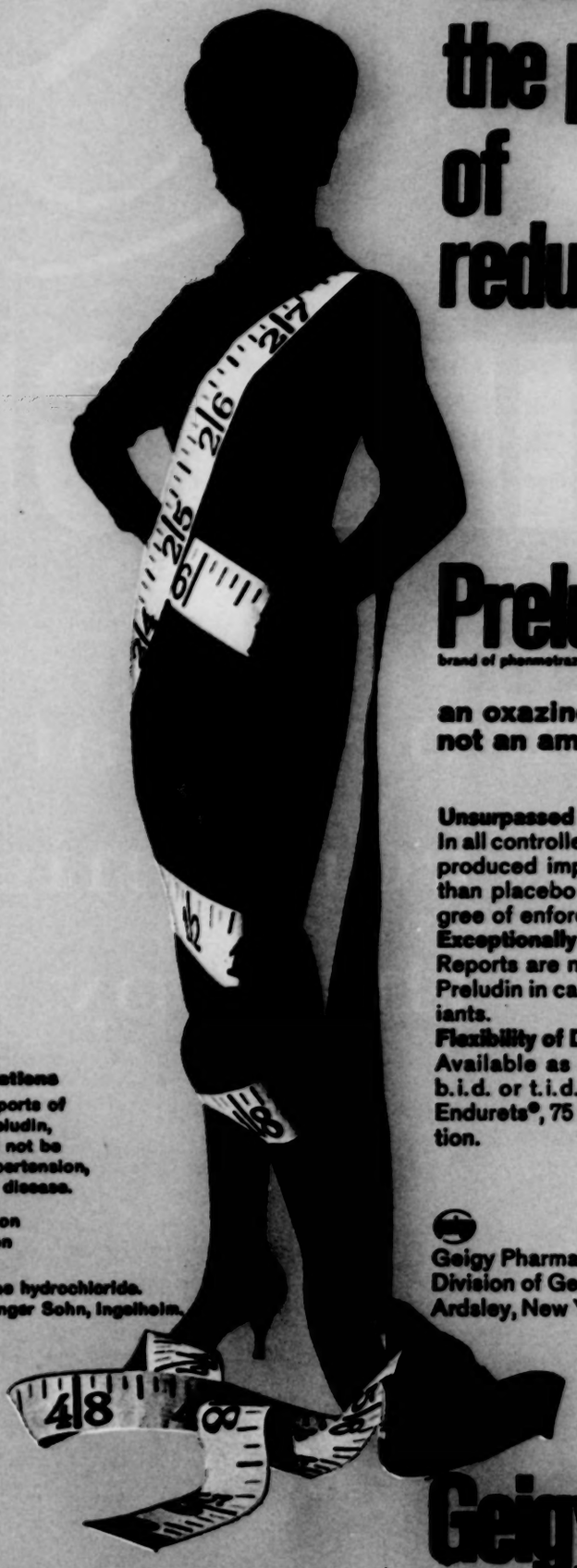
New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being®

now available:

Antivert syrup

Each teaspoonful (5 cc.) contains 6.25 mg. meclizine HCl and 25 mg. nicotinic acid.

reducing the problems of reducing



Preludin®

Tablets and Endurets®
prolonged-action tablets

brand of phenmetrazine HCl

**an oxazine...
not an amphetamine**

Unsurpassed Effectiveness
In all controlled clinical studies, Preludin has produced impressively greater weight loss than placebo tablets regardless of the degree of enforcement of dietary restriction.

Exceptionally High Tolerance
Reports are numerous of successful use of Preludin in cases intolerant of other anorexiants.

Flexibility of Dosage
Available as scored tablets of 25 mg. for b.i.d. or t.i.d. administration and also as Endurets®, 75 mg., for once daily administration.

Precautions and Contraindications
Although there have been no reports of significant toxic reactions to Preludin, on theoretical grounds it should not be given to patients with severe hypertension, thyrotoxicosis or acute coronary disease.

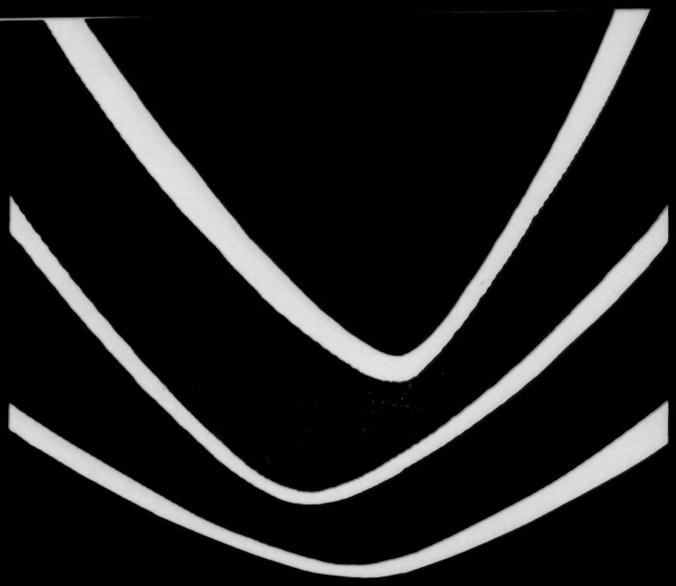
Preludin may be used with caution in cases of moderate hypertension and cardiac decompensation.

Preludin®, brand of phenmetrazine hydrochloride.
Under license from C. H. Boehringer Sohn, Ingelheim.

Geigy Pharmaceuticals
Division of Geigy Chemical Corporation
Ardsley, New York

Geigy

PR 877-61



TRIMAGILL®*

a new, rational,
convenient
therapy for

WHAT IS TRIMAGILL?

Trimagill is presented as a powder for insufflation and as dry, non-greasy vaginal inserts containing Tartaric Acid, Citric Acid, Boric Acid, Dextrose, Potassium Bitartrate, Potassium Alum, and Adhesives.

TRIMAGILL IS LOGICAL!

Pathogenic micro-organisms that cause vaginal infections are incapable of surviving or propagating in a low pH environment. Trimagill produces and maintains a vaginal pH of 2.0 to 2.5—thus, infecting organisms are destroyed because an unfavorable environment is created.

TRIMAGILL IS EFFECTIVE!

Trimagill's low pH favors the growth of beneficial Döderlein bacilli and helps restore vaginal flora following infections. *Unlike antibiotics Trimagill does not foster monilia overgrowth. Resistant strains cannot develop.*

TRIMAGILL IS PRACTICAL AND CONVENIENT!

Trimagill Powder adheres to the vaginal mucosa for several hours *—eliminates need for vaginal and introital packs or external pads.* Trimagill Powder is easily applied during office visits; Trimagill Vaginal Inserts are recommended for patient use between office visits.

UNINTERRUPTED MEDICATION!

Trimagill treatment may safely be continued during menstruation thus preventing the normal physiological change from an acid to an alkaline pH.

TRIMAGILL IS SAFE!

No untoward reactions have been reported in over 3,000 cases treated to date. The combination of ingredients in Trimagill produces an unusually low pH *with emollient properties that prevent irritation of mucous membranes.*

TRIMAGILL IS PROVED BY CLINICAL EXPERIENCE!

Published papers† representing years of clinical experience in over 3,000 patients demonstrate the effectiveness and safety of Trimagill. Trimagill was used successfully in these cases primarily for acidification of the vaginal tract in treatment of vaginal infections. It was also used and is recommended as a non-absorbable agent following conization of the cervix to help eliminate postoperative sloughing, perineal odor, absorb secretion and maintain an acid pH.

TRIMAGILL IS SUPPLIED:

As *Powder: 5* oz. Plastic Insufflator Bottles; *As Vaginal Inserts:* Boxes of 24. NOTE: Consult package circular for full details on instructions for use of both Powder and Vaginal Inserts.

WRITE FOR SAMPLES AND REPRINTS

*Patent Applied For.

†Reprints of published papers available on request.

E. MASSENGILL COMPANY

Bristol, Tennessee

Kansas City • San Francisco • New York

Lifts depression...as it calms anxiety!

Smooth, balanced action lifts depression as it calms anxiety...rapidly and safely

Balances the mood – no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient – *they often aggravate anxiety and tension.*

And although amphetamine-barbiturate combinations may counteract excessive stimulation – *they often deepen depression.*

In contrast to such "seesaw" effects, Deprol's smooth, *balanced* action lifts depression as it calms anxiety – both at the same time.

Acts swiftly – the patient often feels better, sleeps better, within a few days. Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly – often within a few days. Thus, the expense to the patient of long-term drug therapy can be avoided.

Acts safely – no danger of liver damage. Deprol does not produce liver damage, hypotension, psychotic reactions or changes in sexual function – frequently reported with other antidepressant drugs.

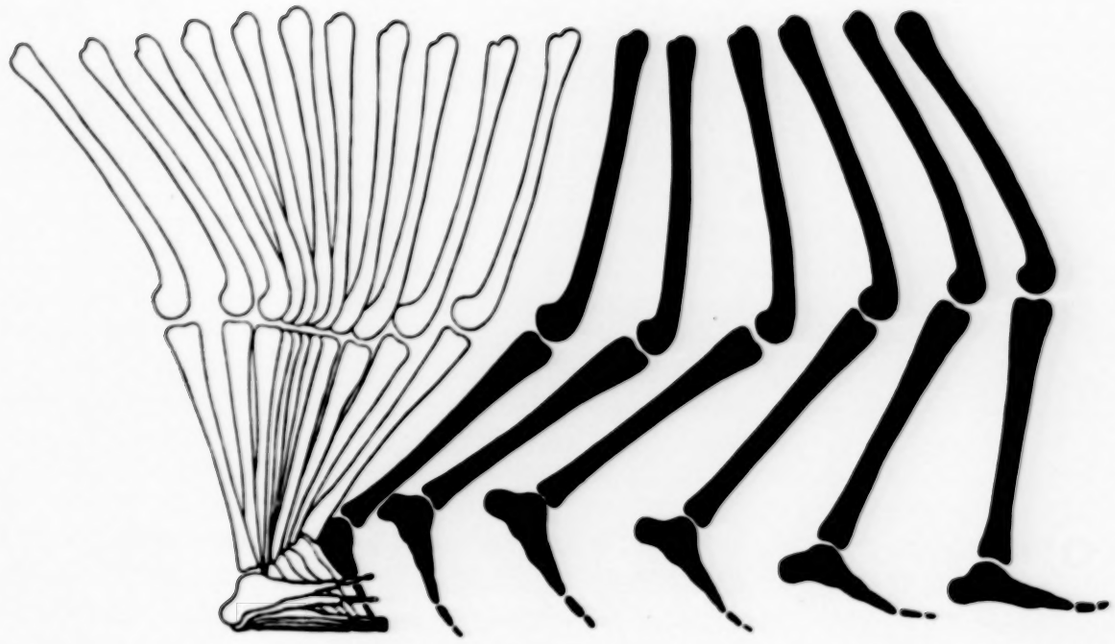
Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate. **Supplied:** Bottles of 50 light-pink, scored tablets. Write for literature and samples.

▲Deprol▲®

WALLACE LABORATORIES/*Cranbury, N. J.*

69-2125



Depo-Medrol was administered intra-articularly to 118 patients (250 injections) for disorders including rheumatoid arthritis, osteoarthritis, epicondylitis, and tendinitis.

Relief of pain and swelling was marked or complete in 104 of the 118 (88.1%); duration of response to a single injection was more than three weeks in 89 patients (75.4%) and more than six weeks in 39 of these.[1] "Post-injection flare-up was practically non-existent."[1]

Indications and dosages

Intra-articular, intrabursal and intratendinous injections of Depo-Medrol are useful for sustained anti-inflammatory effect and symptomatic relief in rheumatoid arthritis, osteoarthritis, bursitis, tendinitis, epicondylitis and other rheumatic disorders.

Intra-articular dosage depends on the size of the joint and the severity of the condition. Injections may be repeated, if necessary, at intervals of one to five weeks. A suggested dosage guide: Large joint, 20 to 80 mg.; medium joint, 10 to 40 mg.; small joint, 4 to 10 mg.

For administration directly into bursae, dosage may be 4 to 30 mg. (repeat injections are usually not needed).

For injection into the tendon sheath, 4 to 30 mg. is a usual range (in recurrent or chronic conditions, repeat injections may be needed).

Precautions

Depo-Medrol for local effect is contraindicated in the presence of acute infectious conditions. Infrequently, atrophic changes in the dermis may form shallow depressions in the skin at the injection site, but these usually disappear in a few months.

Depo-Medrol 40 mg. per cc.
Each cc. contains:

Medrol (methylprednisolone) acetate	40 mg.
Polyethylene glycol 4000	29 mg.
Sodium chloride	8.7 mg.
Myristyl-gamma-picolinium chloride	0.19 mg.
Water for injection	q.s.

Supplied: 1 cc. and 5 cc. vials

20 mg. per cc.
Each cc. contains:

Medrol (methylprednisolone) acetate	20 mg.
Polyethylene glycol 4000	29.6 mg.
Sodium chloride	8.9 mg.
Myristyl-gamma-picolinium chloride	0.19 mg.
Water for injection	q.s.

Supplied: 5 cc. vials

1. Norcross, B. M., and Winter, J. A.: Methylprednisolone acetate: a single preparation suitable for both intra-articular and systemic use, New York J. Med. *61*:552 (Feb. 15) 1961.

*Trademark, Reg. U. S. Pat. Off. methylprednisolone acetate, Upjohn

The Upjohn Company, Kalamazoo, Michigan

Upjohn

relief within hours... lasting for weeks

Depo-Medrol* intra-articularly

Medrol hits the *disease*, but spares the *patient*.

designed
with a
specific
aim

BENYLIN EXPECTORANT

specifically designed to help control cough

Just as a medical instrument is engineered for maximum efficiency in performing its specific function, BENYLIN® EXPECTORANT is formulated to provide effective relief of cough associated with colds or allergy.

This outstanding antitussive action of BENYLIN EXPECTORANT is attributed to a carefully selected combination of therapeutic agents. Benadryl,® a potent antihistaminic-antispasmodic, reduces bronchial spasm, quiets the cough reflex, and lessens nasal stuffiness, sneezing, lacrimation, itching, and other allergic manifestations. Concurrent respiratory congestion is relieved by expectorant agents that efficiently break down tenacious mucosal secretions. In addition, a demulcent action soothes irritated throat membranes. 50461

BENYLIN EXPECTORANT is a pleasant-tasting, raspberry-flavored syrup... completely acceptable to patients of all ages.

supplied: BENYLIN EXPECTORANT is available in 16-ounce and 1-gallon bottles.

Each fluidounce contains: 80 mg. Benadryl hydrochloride (diphenhydramine hydrochloride, Parke-Davis); 12 gr. ammonium chloride; 5 gr. sodium citrate; 2 gr. chloroform; 1/10 gr. menthol; and 5% alcohol. *Indications:* Relief of coughs due to colds, and other symptoms associated with colds, and coughs of allergic origin. *Dosage:* Adults—1 to 2 teaspoonfuls every three to four hours. Children—½ to 1 teaspoonful every four hours. *Precautions:* Products containing Benadryl should be used cautiously with hypnotics or other sedatives; if atropine-like effects are undesirable; or if the patient engages in activities requiring alertness or rapid, accurate response (such as driving).

PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigan

NEW...

LE-test™

a rapid slide screening test for

Systemic Lupus Erythematosus

This simple test has demonstrated a high degree of specificity for the antinuclear factors associated with systemic lupus erythematosus (SLE). Latex-Nucleoprotein Reagent (prepared from polystyrene latex and desoxyribonucleoprotein) reacts clearly and speedily with one drop of serum from patients with active SLE. It does not react with serum from patients with classic rheumatoid arthritis.

In addition to helping differentiate SLE from other collagen diseases, LE-TEST is particularly useful as an aid in ruling out SLE as the cause of unexplained or non-specific signs and symptoms.

LE-TEST is now available for your laboratory.

Hyland Laboratories

4501 Colorado Blvd., Los Angeles 39, Calif.
Branch office: 160 Lockwood Ave., Yonkers, N.Y.

Other Hyland latex-fixation rapid slide screening tests: RA-TEST® **for detection of rheumatoid factor in rheumatoid arthritis;** GG-TEST® **for detection of agammaglobulinemia;** CR-TEST® **for detection and quantitation of C-reactive protein;** FI-TEST® **for detection of hypofibrinogenemia;** TA-TEST® **for detection of thyroglobulin autoprecipitin associated with Hashimoto's thyroiditis;** Latex-Trichina Reagent, **for detection of trichinosis.**

Put your low-back patient back on the payroll

Soma's prompt relief of pain and stiffness can get your low-back patients back to work in days instead of weeks

Soma is unique because it combines the properties of an effective muscle relaxant and an independent analgesic in *a single drug*. Unlike most other muscle relaxants, which can only relax muscle tension, Soma attacks both phases of the pain-spasm cycle at the same time.

Thus with Soma, you can break up both pain and spasm fast, effectively . . . help give your patient the two things he wants most: relief from pain and rapid return to full activity.

Soma is notably safe. Side effects are rare. Drowsiness may occur, but usually only with higher dosages. Soma is available in 350 mg. tablets. Usual dosage is 1 tablet q.i.d.

The muscle relaxant with an independent pain-relieving action

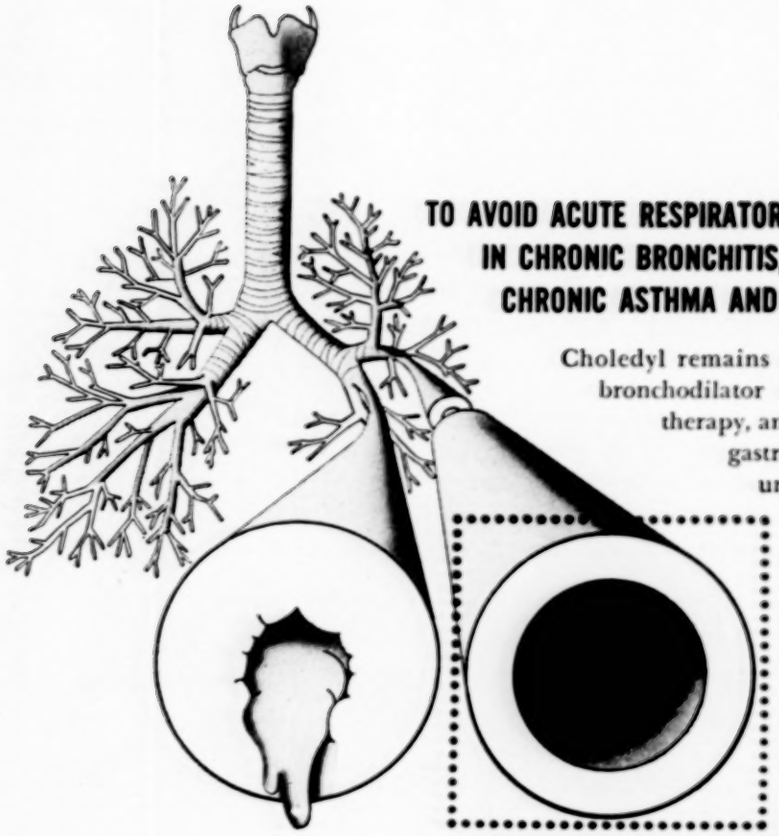
SOMA®

(carisoprodol, Wallace)

Wallace Laboratories, Cranbury, New Jersey

How you can help save your patients a month's pay

Kestler reports in J.A.M.A. (April 30, 1960) that conventionally treated low-back syndrome patients required an average of 41 days for full recovery (range: 3 to 90 days). The addition of Soma therapy in this comparative investigation reduced the average to 11.5 days (range: 2 to 21 days). With Soma, patients averaged full recovery 30 days sooner.



TO AVOID ACUTE RESPIRATORY DISTRESS IN CHRONIC BRONCHITIS, CHRONIC ASTHMA AND EMPHYSEMA

Choledyl remains a uniformly effective bronchodilator throughout prolonged therapy, and it is virtually free of gastric irritation and other unwanted effects *even in geriatric patients.*

SUPERIOR BRONCHODILATATION THROUGH SUPERIOR THEOPHYLLINE ABSORPTION

Choledyl is often effective when aminophylline or other xanthines fail, because it produces up to 75% higher theophylline blood levels than equivalent doses of aminophylline. Depend on Choledyl to relieve bronchospasm, coughing and wheezing . . . to increase vital capacity . . . to ease expectoration.

CHOLEDYL®

THE CHOLINE SALT OF THEOPHYLLINE

brand of oxtriphylline

betters breathing . . . decreases wheezing

WARNER CHILCOTT

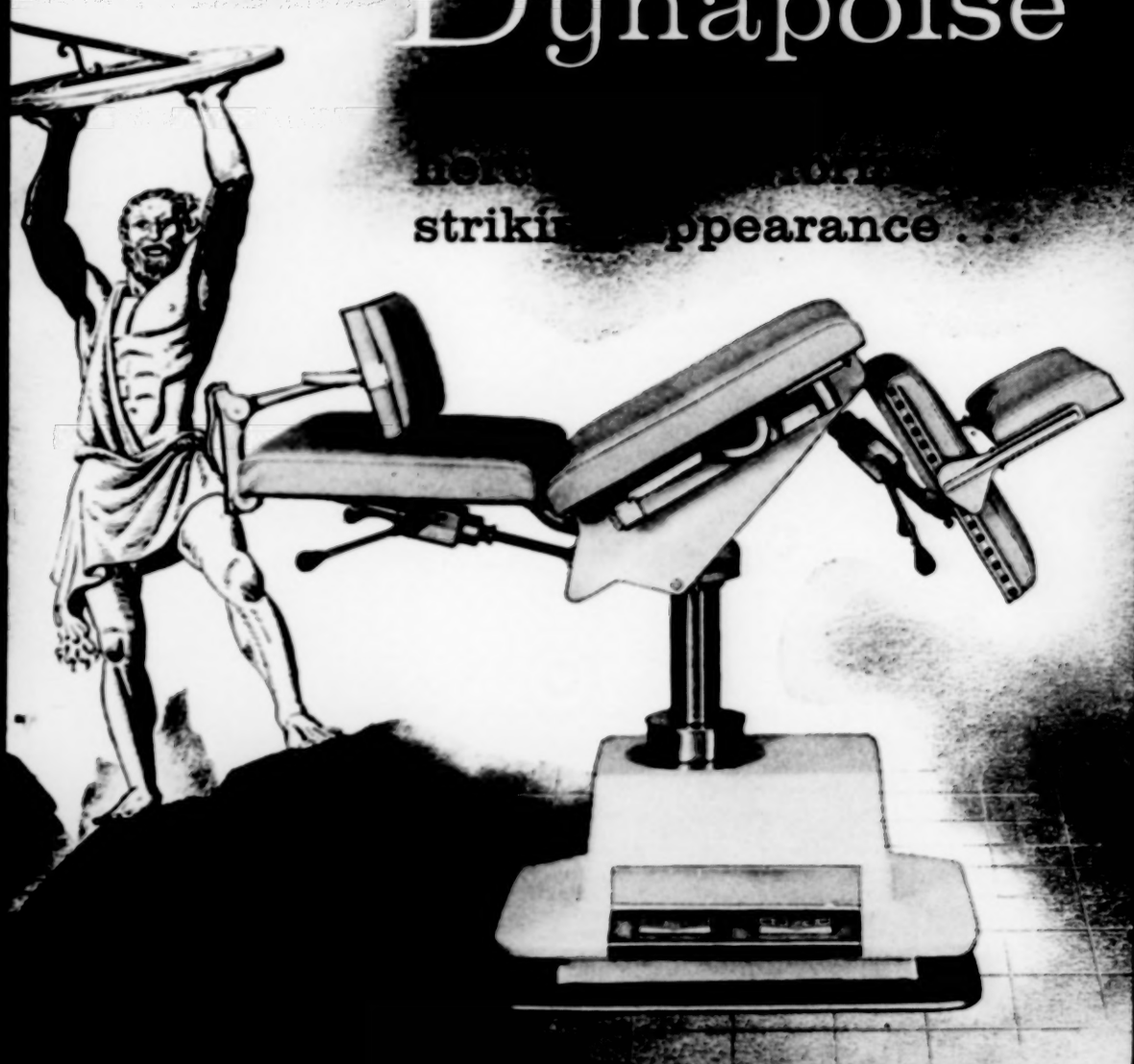
MORRIS PLAINS, N.J.

Supplied: 200 mg. tablets (yellow); bottles of 100. Full dosage information, available on request, should be consulted before initiating therapy.

6P11

makers of TEDRAL GELUSIL PROLOID PERITRATE MANDELAMINE

AMSCO Dynapoise



...without equal in performance, ...energy. Its complete versatility of smooth ...ible you to examine and treat MORE patients ... your patients will be more comfortable, relaxed, and ... and YOU will be less tired at the end of "hours."

...the new powerized Examining and Treatment Table for office and clinic, is a logical projection of the continuing research that produced, and is producing, the world's most favored surgical operating tables.

Dynapoise is clearly destined to become "standard" for modern medical offices. May we suggest that you investigate its physician-oriented advantages . . . now? Mail the coupon for eight-page Brochure PD-703.

AMERICAN STERILIZER
ERIE • PENNSYLVANIA

World's largest designer and manufacturer of Sterilizers, Operating Tables, Lights and related equipment

• Please send illustrated Brochure PD-703 detailing full range of Dynapoise power positioning and time-energy saving features.

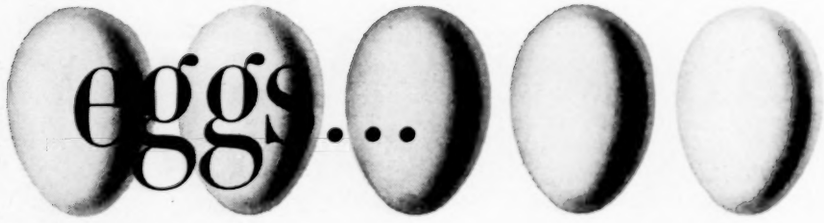
Name _____

Address _____

City and State _____

Mail to American Sterilizer Co., Erie, Pa.

'62



and the fat recommendation in current dietary thinking

Cholesterogenesis in man is recognized as a highly complex process, only partially affected by the character of the diet. Nonetheless, the opinion is often expressed that the lipid content of the adult American diet might well be reduced from its current level of 40 to 50% of daily calories to about 30%.

The ultimate goal of this recommendation is the possible reduction of serum cholesterol levels.

Because eggs constitute an important part of protein, vitamin, and mineral nutrition, they are included in virtually every authoritative low fat diet. In a diet supplying 2500 calories, 30% of which are furnished by lipids, the lipids of two eggs comprise only 1/7 of the allowed daily fat intake.

Two Eggs Provide*:

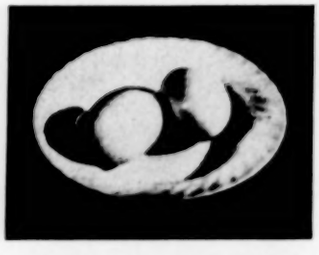
Protein	13 Gm.
Carbohydrate	1 Gm.
Fats (total lipids)	12 Gm.
Fatty acids	
Saturated (total)	4 Gm.
Unsaturated	
Oleic acid	5 Gm.
Linoleic acid	1 Gm.

Vitamins present: A, D, E, K, B_1, B_2, B_6, B_{12}, pantothenic acid, niacin, folic acid, biotin.

Minerals present: Calcium, phosphorus, sodium, potassium, chlorine, sulfur, iron, iodine, manganese, magnesium, zinc, copper.

**U. S. Department of Agriculture Home and Garden Bulletin No. 72, Sept. 1960.*

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.



Poultry and Egg National Board
8 South Michigan Avenue, Chicago 3, Ill.

Treating a respiratory allergy patient...with little response?

try NORISODRINE® syrup

(Isoproterenol Sulfate, Abbott)

with calcium iodide

You've seen the type. Racked by a chronic cough . . . or wheeze . . . or any of the other classic asthma symptoms. In any event, the usual treatment isn't affording adequate relief.

If you're faced with this kind of "problem" patient, try this: Put him on Norisodrine Syrup for two weeks—one or two teaspoonfuls, four to six times daily. See if this isn't evident:

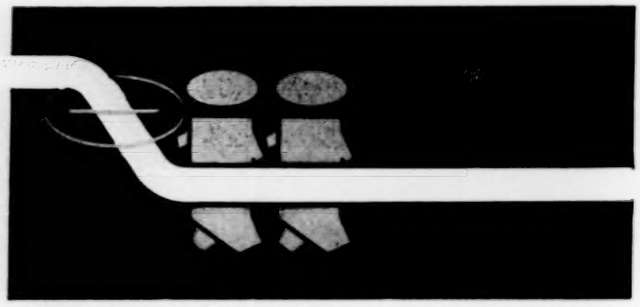
Coughing will be more productive . . . and much less frequent. There will be a marked lessening of tension, physical and mental. Respiration will improve. Nighttime cough, particularly, will be relieved.

Good-tasting Norisodrine Syrup—a combination of Norisodrine (bronchodilator) and calcium iodide (expectorant)—can help you control symptoms in patients of all ages, even those who have been troubled for years.

ABBOTT

104220

HOW CAN THE FULL POTENTIAL OF ORAL THERAPY BE REALIZED?



Diabinese®
BRAND OF CHLORPROPAMIDE

the oral antidiabetic most likely to succeed

The superior effectiveness of chlorpropamide (DIABINESE) is indicated not only by its success in patients in whom tolbutamide has failed,[1,2] but also by its ability to maintain effective control even when carbohydrate intake is increased because of a more liberal diet.[3] Underscoring this superiority in oral therapy, Hamwi and Skillman[4] observe that in diabetics suitable for sulfonylurea therapy, DIABINESE, "with its more constant blood levels and slower degradation would appear to be the choice in patients predictably less likely to respond because of a clinically more severe state of diabetes."

1. A.M.A. Council on Drugs: New and Nonofficial Drugs 1961, Philadelphia, Lippincott, 1961, p. 657. 2. Jackson, D., and Oakley, W.: Lancet 2:752, 1959. 3. Blöch, J., and Lenhardt, A.: Ann. New York Acad. Sc. 74:954, 1959. 4. Hamwi, G. J., and Skillman, T. G.: Postgrad. Med. 27:687, 1960.

FOR MAXIMAL ASSURANCE OF CONTINUOUS BLOOD-SUGAR CONTROL WITH ORAL THERAPY—DIABINESE

to realize the full potential of oral therapy

to replace or reduce insulin dosage

to ensure control where diet alone has failed

IN BRIEF

DIABINESE, a potent sulfonylurea, provides smooth, long-lasting control of blood sugar permitting economy and simplicity of low, once-a-day dosage. Moreover, DIABINESE often works where other agents have failed to give satisfactory control.

INDICATIONS: Uncomplicated diabetes mellitus of stable, mild or moderately severe nonketotic, maturity-onset type. Certain "brittle" patients may be helped to smoother control with reduced insulin requirements.

ADMINISTRATION AND DOSAGE: Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

Like insulin, DIABINESE dosage must be regulated to individual patient requirements. Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used; most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage information.

SIDE EFFECTS: In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, DIABINESE should be discontinued.

PRECAUTIONS AND CONTRAINDICATIONS: If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since DIABINESE is not significantly metabolized and is excreted slowly. DIABINESE as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function. DIABINESE may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on DIABINESE drink alcoholic beverages.

SUPPLIED: As 100 mg. and 250 mg. scored chlorpropamide tablets.

More detailed professional information available on request.

Science for the world's well-being® **Pfizer**

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York

urge your patients to drink

orange juice

A rich natural source of potassium is important to you and your patients because potassium deficiency has become a serious, recurrent problem in the modern-day treatment of many diseases.

Several valuable new drugs unfortunately drain the body of potassium. Patients receiving these preparations run the danger of a potassium deficiency severe enough to disturb renal function and cause or aggravate edema. Supplementary potassium, therefore, preferably from a rich natural source like Florida orange juice, should always accompany vigorous, prolonged treatment with therapeutic agents of this type.

What better way is there to supply this necessary potassium than for your patient to drink a glass of orange juice each time he takes his medication? . . . What pleasanter source of potassium than delicious, refreshing *Florida orange juice* — either freshly squeezed, frozen, or canned? In any form orange juice is rich in potassium and vitamin C. For the heart failure patient it's important, too, that supplementary potassium tends to reduce the intensity of sodium retention and lessens the threat of edema.

Every 8-ounce glass of Florida orange juice, whether from concentrate or from fresh oranges, contains approximately 446 mg. potassium.

☼

FLORIDA CITRUS COMMISSION, LAKELAND, FLORIDA

NEW 8th EDITION

8 MODERN DRUG ENCYCLOPEDIA

and Therapeutic Index with monthly supplement MODERN DRUGS

The only complete reference on new as well as established products.

Quickly answers questions about ethical pharmaceuticals.

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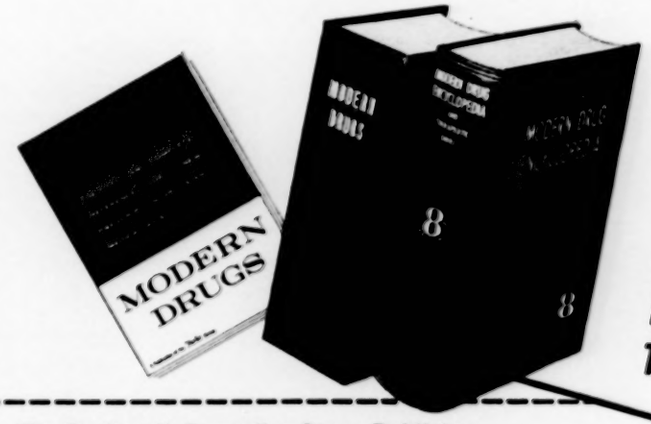

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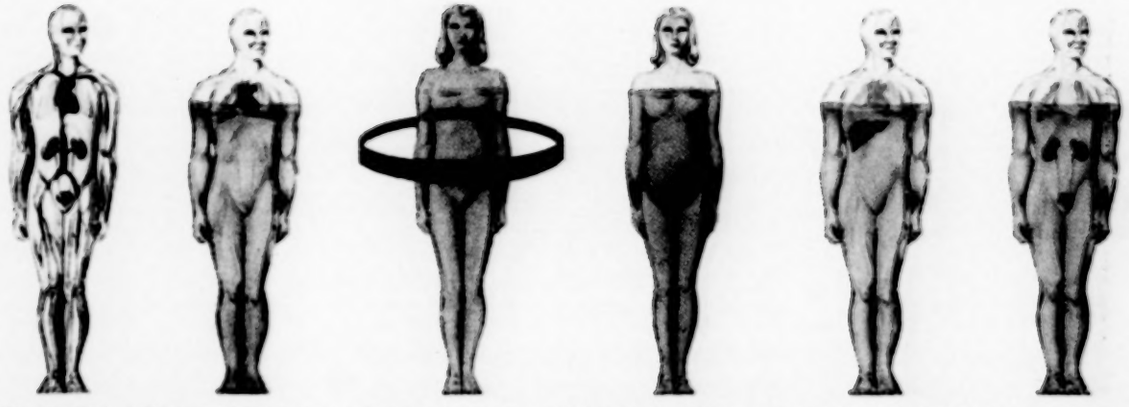

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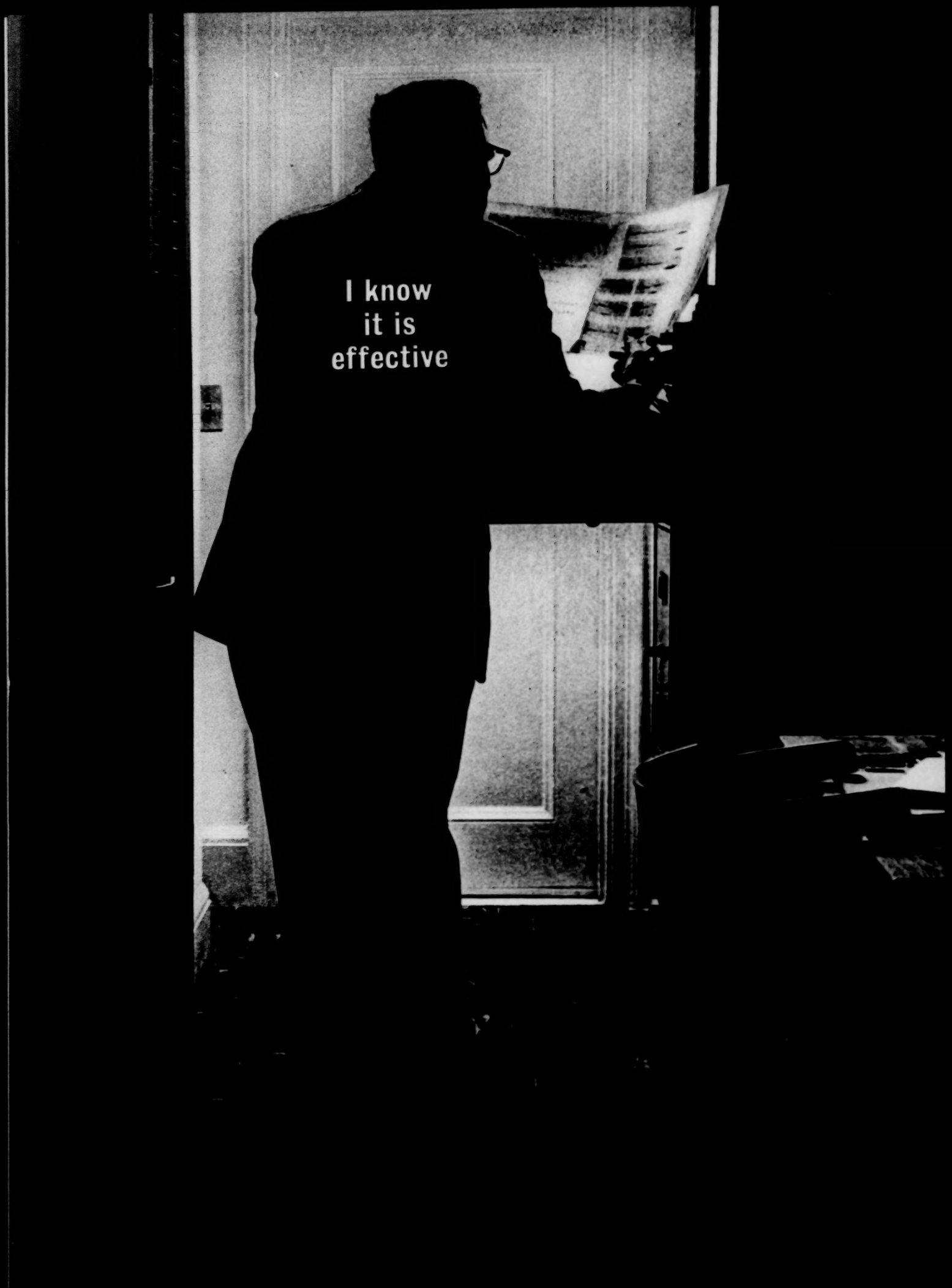
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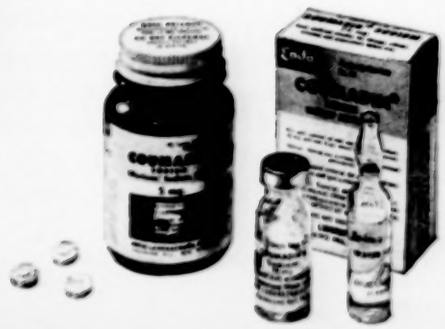

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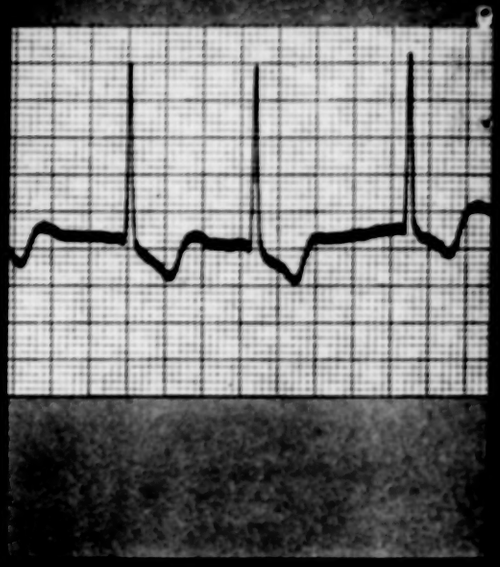

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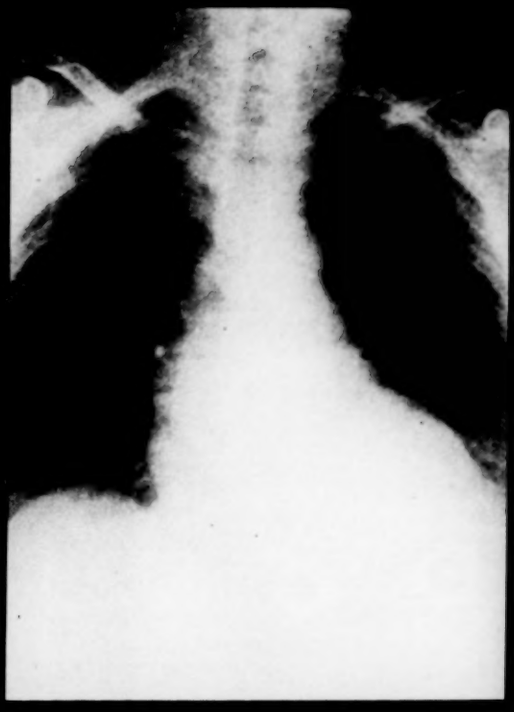

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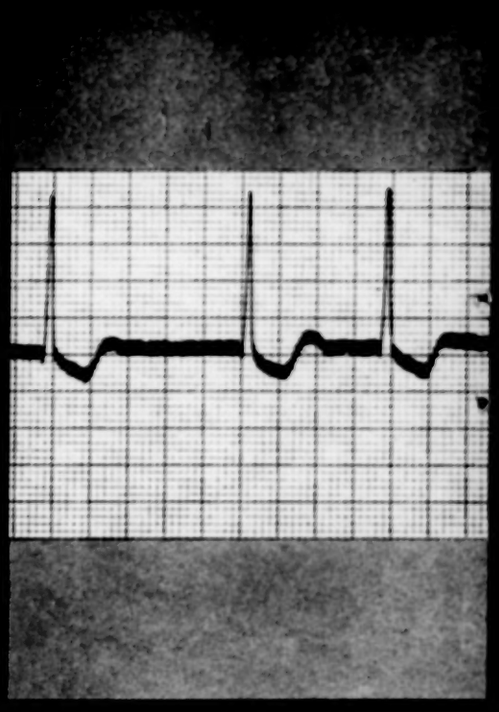

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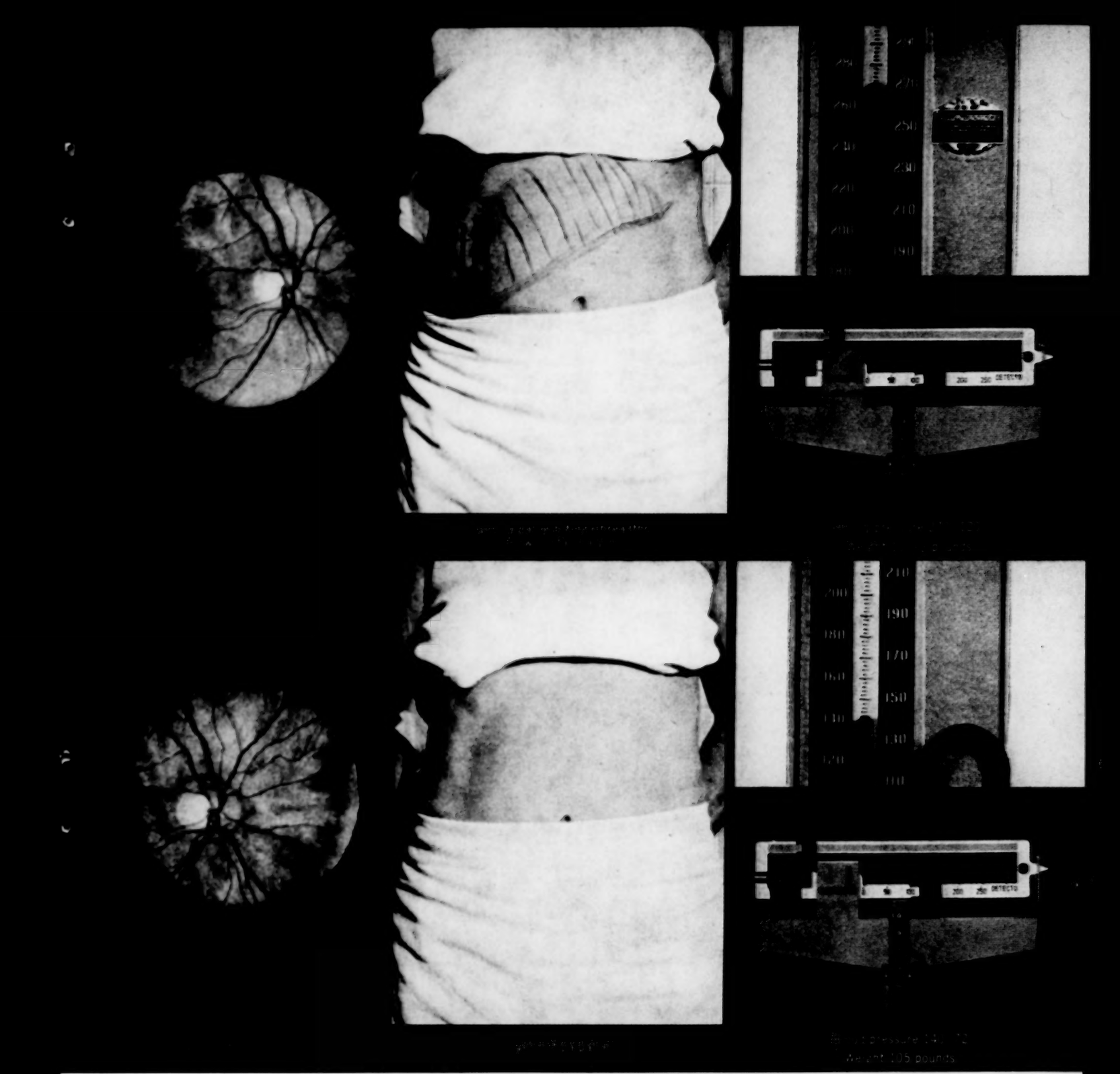

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